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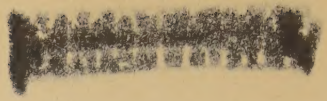




FIG. 1.—Distribution of sympathetic and parasympathetic nerves. The sympathetic nerves and ganglia are illustrated in white, the vagus and parasympathetic nerves in dotted lines, and the mixed terminal nerves in darker shade. (Modified from Müller.)

THE
AUTONOMIC NERVOUS
SYSTEM

BY

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ILLUSTRATED WITH 70 ENGRAVINGS



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PREFACE.

INCREASING appreciation of the importance of the autonomic nervous system in health and disease during the past two decades has stimulated interest in its pathological and clinical aspects, resulting in much investigation. The volume of data bearing on the anatomy, physiology, pathology and clinical aspects of this division of the nervous system is relatively enormous. Although the general morphology of the autonomic nervous system and its general anatomical and physiological relationships to the cerebrospinal nervous system are well known, many details of the finer structure of the components of this system and the exact anatomical and physiological relationships of the autonomic neurons await further investigation. The data bearing on the pathological and clinical aspects of the autonomic nervous system available at present, although voluminous, represent only the beginning of investigation in these important fields, many of these data also remain uncorrelated.

An attempt has been made in the present volume, on the basis of both the older and more recent studies, to describe the autonomic nervous system briefly, but adequately, in relation to the organs and tissues innervated through it and in relation to the cerebrospinal nervous system, to point out its developmental and general physiological relationships to the cerebrospinal nervous system, and to set forth the more important pathological and clinical data bearing on the functional relationships of this division of the nervous system in disease.

It is obviously impossible to consider all the physiological, pathological and clinical data available at present, which bear directly or indirectly on the autonomic nervous system, within the limits of a single volume. Furthermore, it is extremely difficult to present all the facts in their true historical setting. The temptation to make undue use of the most recent and best illustrated contributions is ever present. This tends to create the impression that the latest and most detailed work is the most significant, while the original discoveries which led to these later expansions fail to receive the proper credit. The author desires to give due credit to the pioneer investigators, but space has not been adequate to set forth the complete historical background of our present

knowledge regarding the many phases of this important subject. He is also well aware that many important data have been omitted and certain others have been treated inadequately. An attempt has been made, however, to maintain a proper balance between the various phases of the subject, and to correlate the data selected so as to afford as clear a conception as possible of the regulatory control of the visceral functions which is exercised through the autonomic nerves, the importance of such regulatory control under normal physiological conditions, the interaction between the autonomic and cerebrospinal divisions of the nervous system, and the results of autonomic imbalance or other functional disturbances of the autonomic nervous system.

Each chapter as it was written was referred to one or more of the author's colleagues for criticism, and so far as possible, such criticisms have been met. It is hoped that by this means errors of fact have been in a measure eliminated; final responsibility, however, rests with the author.

I desire to express my indebtedness to my colleagues, Drs. C. H. Neilson, D. M. Shoemaker, A. G. Pohlmann, A. O. Shacklee, W. D. Collier and A. H. Kerper, for helpful criticisms of individual chapters, to Mr. M. C. Waddell for reading the entire manuscript, and to Mr. George Kline for the preparation of many of the illustrations. I also wish to acknowledge the courtesy of all the investigators by whose permission illustrations have been used.

A. K.

ST. LOUIS, MO.

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THE AUTONOMIC NERVOUS SYSTEM.

INTRODUCTION.

IN all the higher animals, including man, the nervous system plays an important rôle in the regulation and coördination of the vital processes, as well as in the adjustment of the organism as a whole to its external environment. In general, the vital processes are not subject to voluntary control, but their nervous regulation and coördination is accomplished by means of reflex nervous reactions of varying degrees of complexity, which are carried out through afferent and efferent conducting systems and reflex and coördinating centers. These centers are located mainly within the central nervous system, but reflex and coördinating centers also occur in the walls of certain of the visceral organs, *e. g.*, the gastrointestinal canal, whose motor activities continue in a coördinated manner in the absence of impulses emanating from the central nervous system.

The skeletal or somatic musculature, *i. e.*, all the striated musculature except the cardiac, is subject to voluntary control, although reflex nervous reactions which are purely involuntary play an important part in its general activity. The efferent nerves supplying this musculature are generally regarded as voluntary. The intrinsic musculature of the visceral organs, including the blood vessels, and other smooth muscles throughout the body, *e. g.*, the erector pili and other cutaneous smooth muscles, are not subject to direct voluntary control. The efferent nerves which supply these muscles may be regarded as involuntary. The various glands which are subject to nervous regulation are also supplied by involuntary nerves. The nerves distributed to the visceral organs, blood vessels, glands, etc., have been designated as involuntary, sympathetic, ganglionic, vegetative and autonomic, but none of these terms was ever universally adopted. Neither is there at present any general agreement regarding the terminology employed.

The term involuntary, first applied to these nerves nearly two centuries ago, is inappropriate by reason of the fact that many of the reactions of the so-called voluntary nerves are not subject to voluntary control. Neither are the nerves supplying certain of the visceral organs wholly free from voluntary influences. Voluntary and involuntary reactions, therefore, afford no adequate criteria

for the differentiation of the rest of the peripheral nervous system from that which is essentially voluntary.

The term sympathetic was introduced by Winslow as early as 1732. It was already known that nerves arising from the ganglionated nerve trunks extending along the ventrolateral aspects of the vertebral column supply both the intestine and the heart. By reason of the numerous connections of these nerve trunks, it was assumed that through them one part of the body exerts an influence on other parts. According to the teaching then current, it was assumed that the sympathies of the body are brought about through these nerves. Therefore, Winslow called them the great sympathetics. Because he believed that the vagus and nervous intermedius subserve a similar function, he called these nerves respectively the medium and small sympathetics. The term sympathetic nervous system has long been used in various ways by various authors. Some have extended it to include the entire autonomic system.

Studies of the ganglia in the course of the nerves in question gave rise to the designations, ganglionic nerves and ganglionic nervous system. Johnstone (1764) advanced the theory that voluntary movements are converted into involuntary movements in these ganglia. In accordance with this theory, the nerves through which involuntary movements are controlled were designated as ganglionic nerves. This designation was not confined to the nerves supplying visceral organs, but was also applied to the nerves involved in the involuntary movements of the skeletal muscles, thus the cerebrospinal ganglia were included in the ganglionic nervous system. When, in the course of time, it became known that the cells in the cerebrospinal ganglia belong to afferent nerves, they were excluded from the ganglionic system, but, as the term was employed, it rarely, if ever, excluded all of them.

The term vegetative nervous system was introduced by Bichat (1800, 1801). He conceived of the life of the organism as made up of animal life (*vie de relation*) and organic or vegetative life (*vie de nutrition*). Accordingly, he also assumed the existence of animal and vegetative nerves. According to his conception, the ganglia of the great sympathetic and some of those of the cranial nerves constitute the nervous organs of organic life. Bichat's theory was never generally accepted *in toto*, but it stimulated much discussion which resulted in increased use of the terms ganglionic nerves and ganglionic nervous system for a time. Not infrequently it also led to the use of the terms organic nerves and organic nervous system. The theory advanced by Bichat practically died out about the middle of the nineteenth century and the terms organic nerves and organic nervous system, fell into disuse, but the term "vegetative" survived and has recently been used by some as a substitute for "autonomic."

Although the terms mentioned above were in use, it was not uncommon, during the first half of the nineteenth century, to divide the peripheral nerves into the cerebrospinal nerves with their ganglia and the sympathetic nerves with their ganglia. This terminology was used extensively from the middle of the nineteenth century to about 1885. It was pointed out from time to time that certain branches of the cranial nerves and the visceral branches of the sacral nerves resemble the splanchnic nerves, but the nerves supplying smooth muscle and glands were not definitely grouped into a single system. Involuntary organs and tissues were supplied by both cerebrospinal and sympathetic nerves.

On the basis of their observations on vasomotor nerves, Dastre and Morat (1884) advocated a partial return to the earlier terminology proposed by Winslow, but included under the general head of the sympathetic nervous system certain unnamed branches of the fifth, seventh, ninth and tenth cranial nerves.

The work of Gaskell (1886-1889) contributed largely to a better understanding of the nerves in question. On the basis of extensive morphological studies, he was able to point out that only certain of the cerebrospinal nerves have a visceral ramus. He also pointed out that the efferent fibers in these visceral rami, which he designated collectively as the visceral nerves, arise in the central nervous system in homologous columns of cells which are interrupted by the development of the nerves to the limbs. He regarded the vagus and pelvic nerves as homologous with the hypogastric and splanchnic nerves respectively. This was the first definite statement regarding the outflow of visceral nerves from three regions of the central nervous system, viz.: the cranial, thoracolumbar and sacral. It also showed clearly that the sympathetic system does not receive fibers from all the spinal nerves. Gaskell classified the ganglia on the visceral nerves as: (1) proximal or vertebral, and (2) distal ganglia. The former class included only the ganglia of the sympathetic trunks from the first thoracic segment downward. The latter included: (*a*) the prevertebral ganglia, viz.: the superior cervical, celiac and superior mesenteric ganglia, and (*b*) the terminal ganglia, located in or near the internal organs. He also advanced the theory that certain of the blood vessels, *e. g.*, the vessels of the extremities and possibly others, are innervated not only by the visceral nerves, but also receive vasodilator fibers via the somatic nerves.

Langley and Dickinson (1889) discovered in the action of nicotine a new method of investigating the relationships of nerve fibers to peripheral nerve cells. The results obtained by the use of this method led Langley (1898) to propose a new term for the system of nerves in question. Though not unmindful of its dependence on the rest of the nervous system, he called it the "autonomic

nervous system." In 1921 he wrote, "The word 'autonomic' does suggest a much greater degree of independence of the central nervous system than in fact exists, except perhaps in the part which is in the walls of the alimentary canal. But it is, I think, more important that new words should be used for new ideas than that the words should be accurately descriptive. In any case the old terms have no advantage as descriptive terms."

When the term "autonomic" was introduced by Langley the innervation of smooth muscles and glands was regarded mainly from two points of view. From the one point of view, these tissues were regarded as being supplied in part by cerebrospinal and in part by sympathetic nerves; from the other (Gaskell), they were regarded as being supplied by a single system of nerves which is separated into three parts anatomically by the development of the nerves to the limbs. It was well known that the thoracolumbar outflow through the sympathetic trunks innervates the whole body, but it was assumed that the cranial and sacral outflows innervate only parts of the body. It was also known that the functional effects of the sympathetic are, in general, the opposite of those of the cranial and sacral autonomic nerves. Langley, therefore, regarded the sympathetic as a system distinct from the rest of the autonomic nerves. He also recognized the part of the cranial outflow supplying the eye as distinct from the rest of the cranial outflow. Furthermore, he regarded the bulbar part of the cranial outflow and the sacral outflow as forming one system innervating the alimentary canal and parts developmentally connected with it. Accordingly, he divided the autonomic system into tectal, bulbosacral and sympathetic systems (1898). Later, by reason of the discovery that the effects produced by adrenalin are apparently similar to those produced by stimulation of sympathetic nerves, and that certain other drugs produce effects apparently identical with those produced by stimulation of the tectal and bulbosacral nerves, he grouped the tectal and bulbosacral autonomic nerves together as the parasympathetic system (1905). It had previously been pointed out by Langley (1900) that we should expect the neurons in the myenteric and submucous plexuses to be the post-ganglionic neurons in bulbar and sacral efferent chains, but, since the data available afforded no clear proof of the central connections, of these cells and histological evidence had convinced him that they differ structurally from other peripheral nerve cells, he placed the myenteric and submucous plexuses in a separate system which he designated the enteric nervous system. In 1921 he wrote as follows: "This classification is, I think, still advisable, for the central connection of the enteric nerve cells is still uncertain, and evidence has been obtained that they have automatic and reflex functions which other peripheral nerve cells do not possess."

Most of the earlier investigators in this field on the morphological side supported the theory that the spinal ganglia contain some cells of the sympathetic type and that the sympathetic ganglia contain cells of the type of the spinal ganglion cells. Langley found no evidence of such admixture of the different types of ganglion cells. He regarded the neurons of the sympathetic type as motor. Accordingly, the autonomic nerves, as defined by him, were regarded as purely motor. The afferent nerves accompanying the latter are not in all cases distinguishable from other afferent nerves; consequently, they were not regarded as autonomic.

Although Langley's classification of the nerves in question cannot be regarded as final, and he himself recognized the inadequacy of the terminology which he proposed, it is, doubtless, in its major aspects, the most satisfactory terminology in use at the present time. Furthermore, as Schilf (1926) fittingly suggested, the term autonomic nervous system ought to be used in recognition of Langley's great contribution to our knowledge, especially of the physiology and pharmacology, but also of the anatomy of the system of nerves in question. Accordingly, the terms autonomic, sympathetic and parasympathetic will be used in the present volume in the sense in which Langley used them. Such minor deviations from Langley's classification and terminology as are introduced will be discussed in their proper connections.

CHAPTER I.

MORPHOLOGY AND DISTRIBUTION OF THE AUTONOMIC NERVOUS SYSTEM.

DEFINITION AND TERMINOLOGY.

THE autonomic nervous system may be regarded as the division of the nervous system which includes all the neurons lying outside the central nervous system and cerebrospinal ganglia, except those associated with the special sense organs, and the cells through which these outlying neurons are functionally connected with the central nervous system. Certain centers in the brain stem, which are functionally superimposed on the aggregates of neurons in the central nervous system which send their axons out to the outlying neurons, are also regarded as autonomic centers. The outlying neurons are aggregated in the autonomic ganglia. The connecting neurons are located mainly in the general visceral efferent nuclei in the brain stem and the visceral cell columns (intermediolateral columns) in the spinal cord. Their axons terminate in synaptic relationship to neurons in the outlying ganglia. By reason of this relationship, the former are commonly designated as preganglionic, and the latter as postganglionic neurons. The afferent cerebrospinal nerve components which are functionally associated with these nerves are not commonly regarded as part of the autonomic nervous system. The afferent neurons through which visceral impulses are conveyed to the central nervous system are the general visceral afferent components of the cerebrospinal nerves. Their cell bodies are located in the cerebrospinal ganglia; their peripheral processes traverse the autonomic ganglia without interruption and are not known to enter into direct functional relationship with peripheral autonomic neurons. The distribution of their central processes in the central nervous system is not fully known. It is known, however, that they make direct reflex connections with visceral efferent neurons. In the spinal cord, these connections probably are effected without the intervention of intercalated neurons. The somatic spinal reflex arc comprises at least three elements, viz.: an excitor element, consisting of a neuron in the anterior horn of the spinal cord, which sends its axon to a muscle, a receptor element, consisting of a spinal ganglion cell with its distal process terminating in a peripheral sense organ, and a connector element, consisting of an intercalated neuron lying wholly within the spinal cord. These

connector elements not only associate somatic receptors and excitors in the same level of the spinal cord, but may run up or down in ascending or descending tracts, bringing neurons at different levels into functional relationship. In the autonomic system the outflow of preganglionic fibers represents the connector elements; the post-ganglionic neurons in the autonomic ganglia represent the excitor elements (Fig. 2). Just as the connector elements in the somatic system may ascend or descend in the spinal cord, so the connector elements in the autonomic system may ascend or descend in the

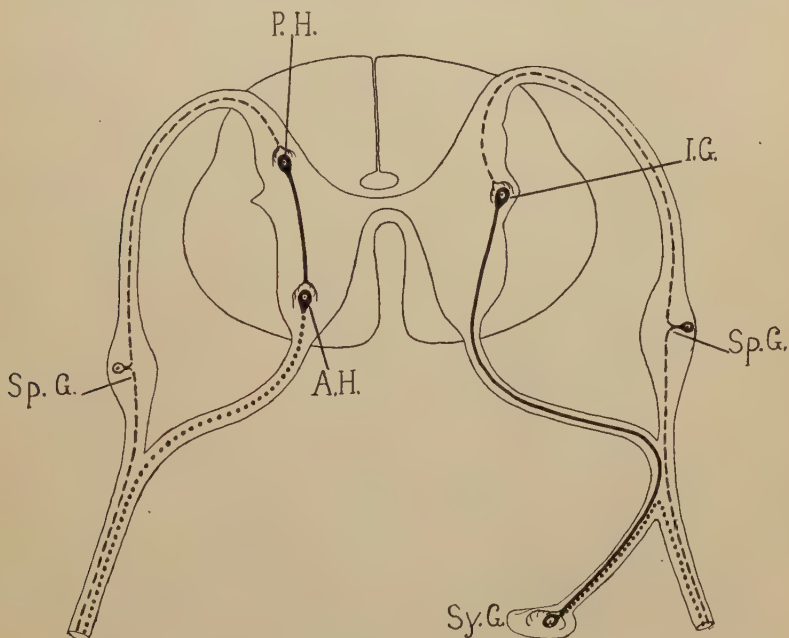


FIG. 2.—Diagrammatic illustration of an ordinary spinal reflex arc (left) and a sympathetic reflex arc (right). *A.H.*, anterior horn cell; *I.G.*, visceral efferent cell in intermediolateral column; *P.H.*, posterior horn cell; *Sp.G.*, spinal ganglion cell; *Sy.G.*, sympathetic ganglion. (After Gaskell, *The Involuntary Nervous System*, courtesy of Longmans, Green & Co., Ltd.)

sympathetic trunk. The purpose of this different arrangement in the two systems, doubtless, is correlated with the difference in their functions. Somatic reflexes are localized and accurate, visceral reflexes, in general, produce more or less wide-spread diffuse effects. The arrangement of the preganglionic and ganglionic neurons in the autonomic nervous system adapts it admirably to produce generalized effects easily and speedily.

The above consideration shows clearly that the autonomic nervous system is a functional and not an anatomical division of the

nervous system. The preganglionic neurons lie in part within the central nervous system; the ganglionic neurons are located in the sympathetic and parasympathetic ganglia. According to the origin of the preganglionic fibers from the central nervous system,

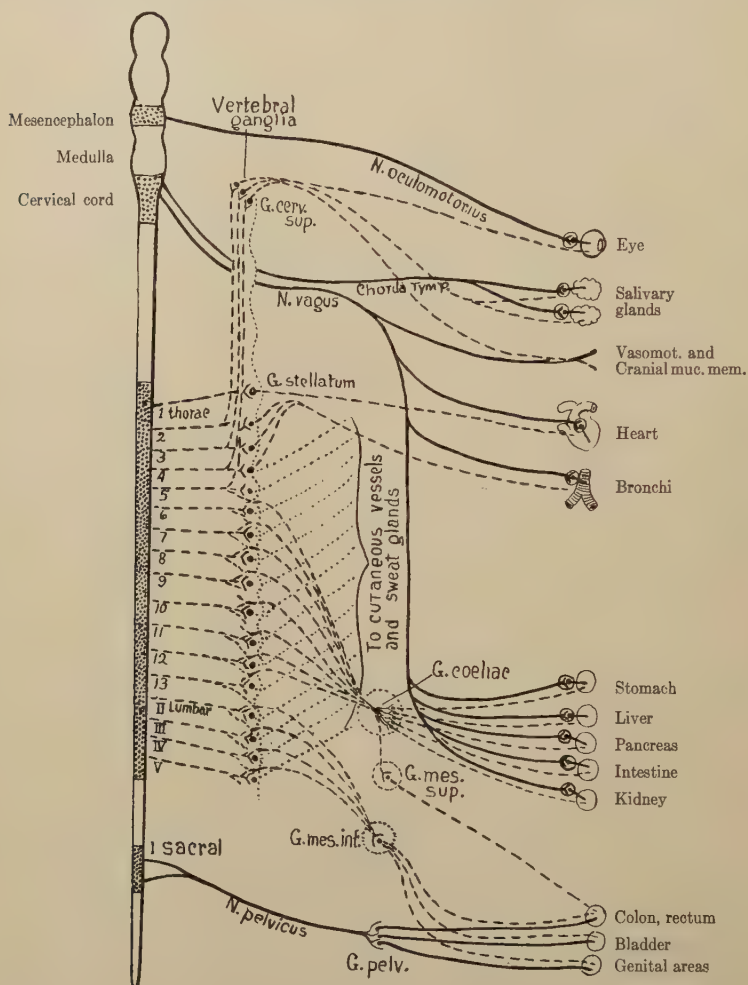


FIG. 3.—Diagram of the autonomic nervous system. The solid black lines represent the cranial and sacral; the broken lines represent the thoracolumbar subdivision. (Modified from Meyer and Gottlieb.)

the autonomic system may be divided into: (1) the cranial autonomic system, whose preganglionic fibers emerge through the third, seventh, ninth, tenth and eleventh cranial nerves; (2) the thoracolumbar autonomic system, whose preganglionic fibers emerge

through the thoracic and upper lumbar spinal nerves; and (3) the sacral autonomic system, whose preganglionic fibers emerge through the second, third and fourth sacral nerves (Fig. 3).

The fibers of the thoracolumbar outflow join the sympathetic trunk through the white communicating rami; those of the cranial and sacral outflows do not join the sympathetic trunk but run directly to the peripheral plexuses. The preganglionic fibers of the thoracolumbar outflow terminate either in the ganglia of the sympathetic trunk or in the prevertebral ganglia; those of the cranial and sacral outflows end in the terminal ganglia. In this respect, as in their response to certain drugs, *e. g.*, adrenalin and atropin, the cranial and sacral outflows agree with each other, but differ from the thoracolumbar outflow. The cranial and sacral systems have been grouped together, on this basis, as the cranio-sacral autonomic system in contrast to the thoracolumbar autonomic system. The former constitutes the parasympathetic; the latter the sympathetic system, according to the common usage of these terms.

As stated above, Langley placed the myenteric and submucous plexuses in a separate division which he designated the enteric nervous system. Embryological data which will be presented in Chapter V indicate clearly that these plexuses are related developmentally to the vagus nerves. Embryologically, they may properly be regarded as part of the craniosacral autonomic system. This is also in keeping with the theory advanced by Gaskell in his posthumous work (1916). These plexuses, however, possess a greater degree of functional independence than is known to exist in other parts of the autonomic nervous system. That the enteric nervous mechanism possesses the capacity to carry out coördinated reflex activities in the absence of central nervous influences is now well known. The data on which this statement is based will be discussed in Chapter IX. The neurons in the enteric plexuses cannot be compared directly with those in other peripheral ganglia, *e. g.*, the ganglia of the sympathetic trunk or the cranial autonomic ganglia, since the latter are not known to function except as terminal neurons in visceral efferent chains. It will be advantageous, therefore, by reason of their functional relationships as well as for descriptive purposes, to retain the term enteric nervous system to designate the plexuses in the wall of the alimentary canal.

ANATOMICAL STRUCTURE AND RELATIONSHIPS.

Sympathetic Trunks.—The sympathetic trunks lie along the ventrolateral aspects of the vertebral column and extend from the base of the skull to the coccyx. Each trunk is made up of a series of ganglia (vertebral ganglia) connected by longitudinal fibers.

Except in the cervical region, the ganglia are in general arranged segmentally. They are connected with the spinal nerves through *communicating rami*. These rami include the visceral components of the spinal nerves which are functionally related to the sympathetic system and the sympathetic fibers which join the spinal nerves for distribution to the tissues to be innervated. The spinal nerve components contained in the communicating rami are in the main myelinated and constitute the *white communicating rami*; the sympathetic components, the majority of which are unmyelinated, constitute the *gray communicating rami*. Visceral components are absent in the cervical, lower three lumbar and first sacral nerves. The communicating rami of these nerves, therefore, contain only sympathetic fibers. The sympathetic trunks give rise to visceral nerves through which the internal organs are innervated. These nerves contain visceral afferent, preganglionic and sympathetic fibers.

The cervical portion of each sympathetic trunk lies anterior to the transverse processes of the cervical vertebræ and behind the carotid vessels. It includes the superior, middle (frequently absent), and inferior cervical sympathetic ganglia and contains both myelinated and unmyelinated fibers. The superior cervical, the largest of all sympathetic ganglia, is an elongated cell mass located at the base of the skull between the internal carotid artery and jugular vein and in front of the transverse processes of the second, third and fourth cervical vertebræ. The middle cervical ganglion, when present, is small and is usually situated about the level of the body of the sixth cervical vertebra, but not infrequently occupies a lower position. It commonly lies in front of the inferior thyroid artery, as this artery passes behind the carotid sheath. The inferior cervical ganglion is commonly situated just behind the subclavian artery usually at the point of origin of the vertebral artery. It is usually only imperfectly separated from the first thoracic ganglion, and is sometimes fused with the latter. The two when fused constitute the stellate ganglion (Fig. 4). This ganglion, when present, is situated anterior to the head of the first rib and behind the pleura.

The *superior cervical* sympathetic ganglion is an elongated body which varies considerably in size. It gives rise to gray communicating rami which join the first four cervical nerves. It also sends gray communicating rami to the hypoglossal nerve, the jugular and nodose ganglia of the vagus, and the petrosal ganglion of the glossopharyngeal nerve. A peripheral ramus passes behind the carotid sheath to the wall of the pharynx, where it joins the ascending pharyngeal plexus. A few smaller rami also join the pharyngeal plexus. Not uncommonly one or two small rami are also supplied to the esophagus. The superior cardiac nerve arises near the lower end of the ganglion and descends behind the large vessels, but

usually in front of the superior thyroid artery, and joins the superficial cardiac plexus on the left and the deep cardiac plexus on the right side. According to the recent studies of Coffey, Brown and Humber (1927), the superior cardiac nerve has fibrous connections with the carotid and external maxillary plexuses and, in some instances, with the sympathetic trunk below the superior cervical ganglion. Rarely it also sends a branch to the recurrent nerve. This branch is joined by a branch from the ansa subclavia. A ramus from the superior cervical ganglion also joins the phrenic nerve. Another joins the common trunk of the superior laryngeal nerve before the latter divides into its internal and external branches. In some instances, a ramus which leaves the superior cervical ganglion with the internal carotid nerve also joins the superior laryngeal nerve. The several peripheral rami of the superior cervical ganglion which join the internal carotid artery constitute the internal carotid plexus. These rami give rise to the internal carotid plexus. Other rami join the external carotid artery on which they also form a plexus. The plexuses on the carotid arteries represent the extension of the cervical sympathetic into the head.

The *middle cervical* ganglion (Fig. 4), when present, is usually connected by gray rami with the fifth and sixth, and sometimes also the fourth and seventh cervical nerves. These connections are sometimes absent. In such instances gray rami join these nerves directly from the inferior cervical ganglion or vertebral plexus. The middle cardiac nerve arises from the middle cervical ganglion or, in the absence of this ganglion, from the cervical sympathetic trunk, descends behind the large vessels, either separately or with the other cardiac nerves, and joins the deep cardiac plexus on both sides. Slender rami arising from this ganglion also accompany the inferior thyroid artery to supply the thyroid gland. Another ramus, passing in front of the subclavian artery, forms a loop, the ansa subclavia, and joins the inferior cervical ganglion. Slender rami arising from this loop join the subclavian artery and its branches. In the absence of the middle cervical ganglion, the rami which usually arise from it, arise directly from the interganglionic cord.

The *inferior cervical* ganglion is connected by gray rami with the seventh and eighth cervical and sometimes also the sixth cervical and first thoracic nerves. The inferior cardiac nerve, arising from its medial side, joins the deep cardiac plexus. Slender rami join the plexuses on the subclavian, internal maxillary and vertebral arteries. Fiber bundles derived from the plexus on the vertebral artery join the lower cervical nerves not infrequently as high as the fourth. The vertebral rami of the inferior cervical ganglion may, therefore, be regarded as communicating rami. Not infrequently the inferior cervical ganglion gives rise to a ramus which

joins the recurrent nerve. In some instances rami from this ganglion accompany the common carotid artery and, joining the plexus on the internal carotid artery, contribute to the sympathetic innervation of the head. The subclavian plexus, derived mainly from the

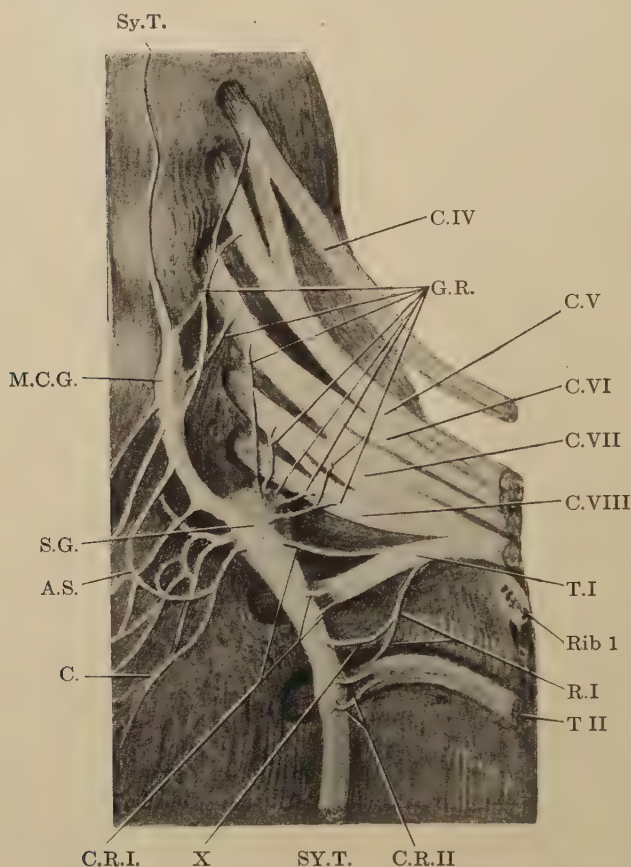


FIG. 4.—Drawing from the cadaver to illustrate the inconstant intrathoracic ramus from the second to the first thoracic nerve and the communicating rami joining the brachial plexus. A.S., ansa subclavia; C., the cardiac nerves; C.IV to C.VIII, cervical nerves; C.R.I., communicating rami to first thoracic nerve; C.R.II., communicating rami to second thoracic nerve; G.R., gray communicating rami to cervical nerves; M.C.G., middle cervical ganglion; S.G., stellate ganglion; Sy.T., sympathetic trunk; X, sympathetic ramus joining the ramus from the second to the first thoracic nerve; T.I, first thoracic nerve; T.II, second thoracic nerve.

ansa subclavia, sends rami to the internal mammary artery and the phrenic nerve.

In the thorax the sympathetic trunk lies behind the pleura and in front of the necks of the ribs from the first to the tenth. This

portion includes ten or eleven ganglia, joined together by longitudinal fibers. In some instances the first thoracic ganglion, rarely also the second, is fused with the inferior cervical to form the *stellate* ganglion. Not infrequently other thoracic ganglia are fused so that the number is still further reduced. The thoracic sympathetic ganglia are usually irregularly angular or fusiform, but vary greatly both in form and size. In general, they are arranged segmentally.

Each thoracic ganglion is connected with the corresponding spinal nerve by a white and a gray ramus. Sometimes these rami are separate, the white ramus usually leaving the spinal nerve distal to the point at which the gray ramus joins it. Sometimes white and gray rami are intimately fused and constitute a single communicating ramus. Not infrequently the sympathetic ganglion is connected with the spinal nerve by more than two rami. Occasionally one of these ganglia may be connected by communicating rami with more than one spinal nerve.

In a large percentage of cases an intrathoracic ramus arising from the second thoracic nerve joins the first usually proximal to the origin of the first intercostal nerve. Not infrequently a gray ramus from the second thoracic sympathetic ganglion joins this ramus. In other cases a gray ramus joins the second thoracic nerve in proximity to the origin of the intrathoracic ramus to the first thoracic nerve (Fig. 4). The latter ramus probably receives sympathetic fibers via the gray ramus to the second thoracic nerve in all cases. Whenever the ramus from the second thoracic nerve joins the first proximal to the origin of the first intercostal nerve, it constitutes a pathway through which sympathetic fibers which leave the sympathetic trunk below the first thoracic ganglion enter the brachial plexus (Kuntz, 1927).

Peripheral rami arising from the upper five thoracic ganglia supply the upper part of the aorta. The second, third and fourth thoracic ganglia also send rami into the posterior pulmonary plexus. The *splanchnic* nerves consist in greater part of visceral afferent and preganglionic visceral efferent fibers which join the sympathetic trunk via the white rami and merely traverse it on their way to more peripheral ganglia. The *greater splanchnic* nerve is formed by the union of several rami arising from the sympathetic trunk between the fifth and ninth or tenth thoracic ganglia (Fig. 5). Descending in the posterior mediastinum, it pierces the diaphragm and joins the coeliac ganglion. A slight enlargement, the splanchnic ganglion, occurs on this nerve opposite the eleventh or twelfth thoracic vertebra. Rami arising both from this ganglion and the nerve join the esophagus and descending aorta. The *lesser splanchnic* nerve is formed by the union of several rami arising usually from the ninth and tenth thoracic ganglia. It pierces the diaphragm in

proximity to the greater splanchnic nerve and, entering the coeliac plexus, terminates in the aortico-renal ganglion. The *lowest*

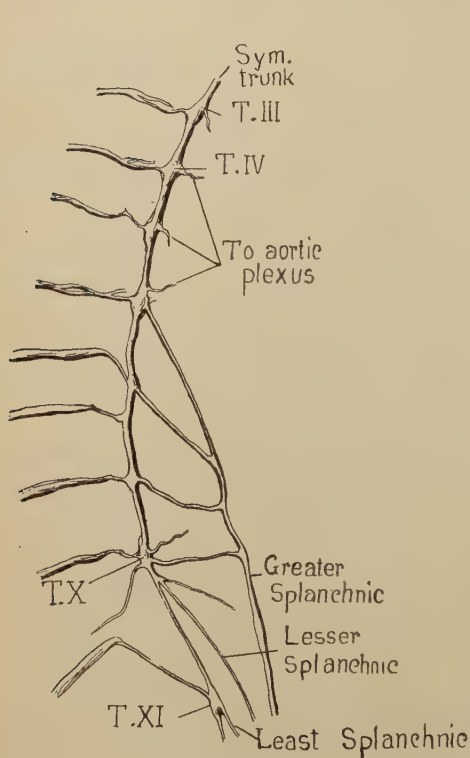


FIG. 5

FIG. 5.—Thoracic sympathetic trunk, communicating rami, rami to aortic plexus, and splanchnic nerves.

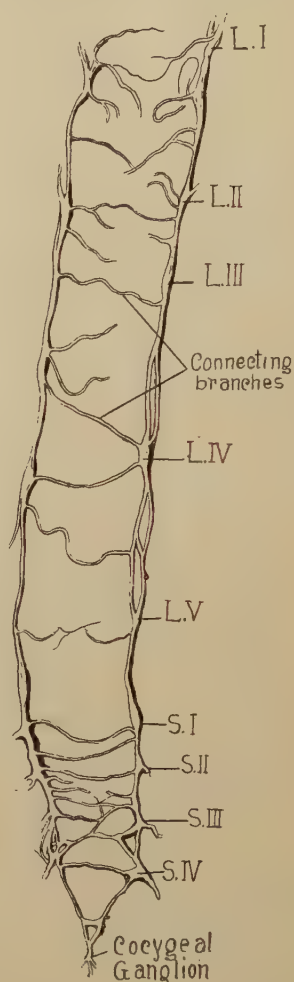


FIG. 6

FIG. 6.—Lumbar and sacral sympathetic trunks. (Drawn from photographs of dissections of human cadavers, by permission of Dr. J. D. Humber.)

splanchnic nerve (sometimes absent) arises from the last thoracic ganglion or the lesser splanchnic nerve, pierces the diaphragm and terminates in the renal plexus.

In the lumbar region the sympathetic trunk lies upon the bodies of the lumbar vertebræ, anterior to the lumbar vessels and medial to the origin of the psoas major muscles. The right and left trunks are connected with each other in this region by numerous connecting rami (Fig. 6). Passing downward from the thorax, it either pierces the diaphragm or lies behind it. At this level it is a very slender cord. The lumbar portion of the sympathetic trunk is extremely variable. It usually includes four ganglia, but not infrequently more than four are present. Occasionally the lumbar ganglia are fused to such an extent that it becomes impossible to recognize individual ganglia. The upper two or three lumbar spinal nerves send white rami into this portion of the sympathetic trunk. It also contains myelinated fibers which enter the trunk through the white rami of the lower thoracic nerves and continue downward. Gray rami arising from the lumbar portion of the sympathetic trunk join all the lumbar nerves. These rami also are extremely variable. One ramus may bifurcate and join two adjacent spinal nerves, or several gray rami (two to five) may join one spinal nerve. Peripheral rami from this portion of the sympathetic trunk also join the aortic plexus.

Continuing into the pelvis, the sympathetic trunk lies on the pelvic surface of the sacrum medial to the anterior sacral foramina (Fig. 6). The right and left trunks are connected with each other by frequent connecting rami. Tending toward the median plane, both trunks usually terminate in the ganglion impar, or coccygeal ganglion, on the surface of the coccyx. This portion of the sympathetic trunk usually includes four ganglia. They are small and gradually diminish in size from above downward. Like the cervical and lower lumbar portions of the sympathetic trunk, this portion receives no white communicating rami. The third and usually also the second and fourth sacral nerves contain visceral components which enter the pelvic plexus via the visceral rami of these nerves without passing through the sympathetic trunk. Gray rami arising from the pelvic portion of the sympathetic trunk join both the sacral and coccygeal nerves. Visceral rami of small size also join the pelvic plexus. A few small parietal rami from both sides form a plexiform network over the pelvic surface of the sacrum.

Prevertebral Plexuses.—The prevertebral autonomic plexuses are situated in the thorax, abdomen and pelvis. Among these the *cardiac*, *celiac*, *hypogastric* and *pelvic* plexuses may be regarded as the great prevertebral plexuses, to each of which smaller plexuses are subsidiary.

The Cardiac Plexus.—The cardiac plexus is situated at the base of the heart and consists of a superficial and a deep part. It is connected with the sympathetic trunks through the superior, middle and inferior cardiac nerves and receives branches of both

vagi. The structure and peripheral distribution of this plexus will be described in Chapter VI.

The Pulmonary Plexuses.—The pulmonary plexuses are continuous with the cardiac plexus, but not subsidiary to it. They are intimately related to the vagus nerves, through which they receive preganglionic fibers. They will be described in detail in Chapter VIII.

The celiac, hypogastric and pelvic plexuses are closely associated with the abdominal aorta and the hypogastric arteries. The subsidiary plexuses extend out on the branches of these arteries and are in the main named after them. They are made up largely of the fibers arising from their intrinsic ganglia and peripheral rami from the lower thoracic, lumbar and upper sacral portions of the sympathetic trunks. Branches of the right vagus nerve also contribute to the celiac plexus and the visceral rami of the second and third or third and fourth sacral nerves join the pelvic plexus without traversing the sympathetic trunk. The hypogastric plexus is continuous with the celiac plexus superiorly and with the pelvic plexus inferiorly. Nerves are distributed through these plexuses to the viscera and vessels of the abdominal and pelvic cavities.

In a recent comparative study of the prevertebral plexuses in man and other primates, Hartmann-Weinberg (1926) pointed out that, although the series of plexuses along the abdominal aorta exhibit a relatively wide range of variation, they consist fundamentally of two paired chains, viz.: a ventral and a lateral pair. Each chain is made up of a metameric series of ganglia connected with each other by interganglionic rami. The several chains are connected with each other and with the sympathetic trunks in a more or less regular manner. They also receive branches of the right vagus and give rise to branches which supply the abdominal and pelvic viscera. The visceral rami of each chain have a more or less definite distribution. Those arising from the ventral chain supply the liver, pancreas, spleen and digestive tube from the abdominal portion of the esophagus to the upper part of the rectum. The lateral chain gives rise to rami which supply the adrenals and the urogenital system. Some of these rami also supply fibers to the large intestine. The aorta and the paired arteries arising from it which extend out to the body wall receive their nerve supply directly from the sympathetic trunks.

The Celiac (Solar) Plexus.—The celiac plexus is the most extensive of the prevertebral plexuses. It is closely associated with the aorta and surrounds the celiac artery. It comprises a dense meshwork of fiber bundles, two large aggregates of ganglion cells, the celiac ganglia, and a number of smaller ganglia. The right and left celiac ganglia lie on the right and left crura of the diaphragm respectively. They receive the greater splanchnic nerves and

constitute the chief ganglionic centers of the cœliac plexus. The lesser splanchnic nerves enter the aortico-renal ganglia which may be regarded as partially detached portions of the cœliac ganglia at their inferior poles.

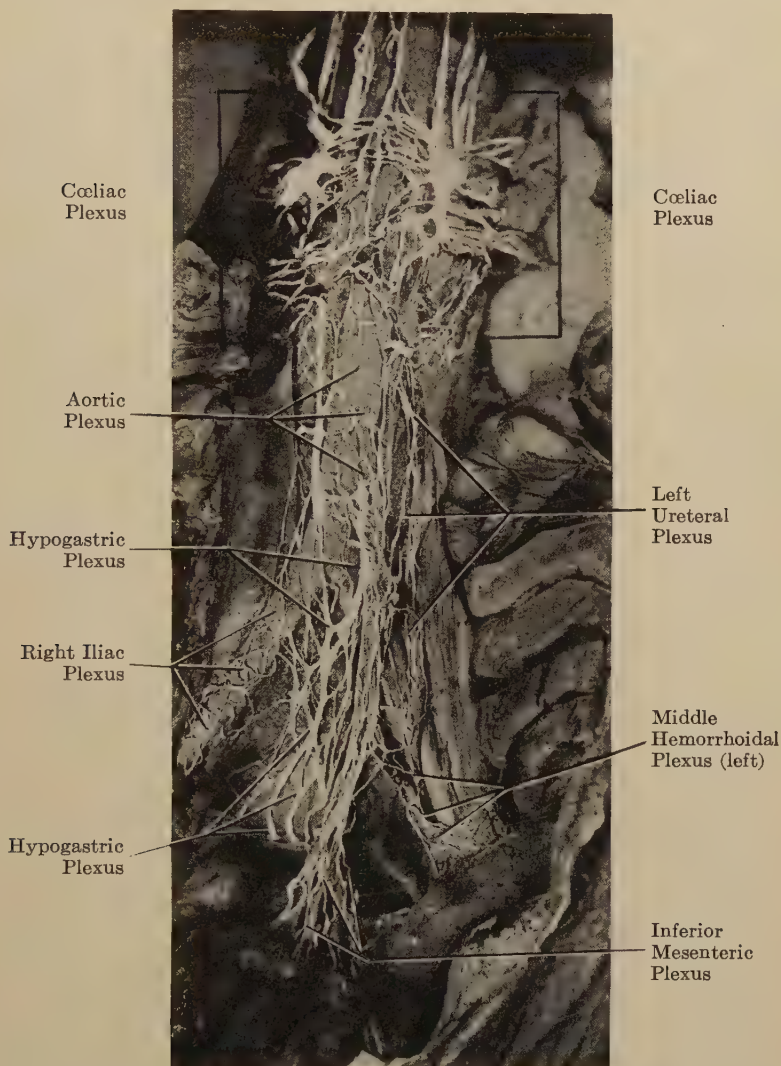


FIG. 7.—Photograph of human dissection. (By permission of Dr. J. D. Humber.)

The cœliac plexus (Fig. 7) invests the cœliac artery throughout its entire length and forms subsidiary plexuses along its branches,

viz.: the *left gastric* plexus, from which rami extend to the esophagus and stomach; the *hepatic plexus*, from which rami extend to the liver and gall bladder, stomach, duodenum and pancreas; and the *splenic* plexus, from which rami extend to the spleen, pancreas and stomach.

Nerves arising from the coeliac ganglia and plexus form subordinate plexuses on the aorta and its branches. The *phrenic* plexus accompanies the inferior phrenic artery. It supplies the diaphragm and gives off rami to the adrenal plexus. On the left side it also supplies rami to the esophagus; on the right, to the inferior vena cava. The *adrenal* plexus accompanies the adrenal artery and sends rami into the substance of the adrenal gland. The *renal* plexus extends laterally along the renal artery to the hilum of the kidney. It is connected with the adrenal plexus and also receives the lowest splanchnic nerve. The *superior mesenteric* plexus accompanies the superior mesenteric artery and forms subordinate plexuses on its branches, through which fibers are supplied to the small intestine, cecum, vermiform appendix and ascending and transverse portions of the colon. This plexus includes the superior mesenteric ganglion and is continuous inferiorly with the aortic plexus. The *aortic* plexus invests the abdominal aorta. It may be regarded as a continuation of the coeliac plexus downward, but it also receives rami from the lumbar sympathetic trunk. It is connected with the hypogastric plexus by the hypogastric nerves. It contributes rami to the adrenal and renal plexuses and gives rise to the spermatic (or ovarian) and the inferior mesenteric plexus. The *spermatic* plexus also receives rami from the renal plexus and extends along the spermatic artery into the spermatic cord and testis. The *ovarian* plexus in the female accompanies the ovarian artery into the pelvis. It supplies rami to the ovary and uterine tube, and, through its communication with the uterine plexus, also supplies fibers to the uterus. The *inferior mesenteric* plexus invests the inferior mesenteric artery and forms subordinate plexuses on its branches, viz.: the colic, sigmoid and superior hemorrhoidal plexuses, through which rami are supplied to the descending colon and the upper part of the rectum (Fig. 7).

The Hypogastric Plexus.—The hypogastric plexus is essentially the connecting link between coeliac and pelvic plexuses. As the hypogastric nerves descend into the pelvis, they break up into numerous bundles which form a plexiform meshwork along the front and back of the bifurcation of the aorta and the region of the common iliac arteries and over the promontory of the sacrum. This meshwork constitutes the hypogastric plexus (Fig. 7).

The Pelvic Plexuses.—The pelvic plexuses represent continuations of the hypogastric plexus along both sides of the rectum. They receive the visceral rami of the second and third or third and fourth

sacral nerves in addition to rami from the upper sacral portions of the sympathetic trunks. Each pelvic plexus gives rise to subordinate plexuses accompanying the hypogastric artery and its branches, viz.: the hemorrhoidal, vesical, prostatic or uterine, and vaginal plexuses, through which fibers are supplied to the pelvic viscera.

Enteric Plexuses.—The intrinsic plexuses of the digestive tube, viz.: the myenteric and submucous plexuses, extend from the upper levels of the esophagus to the anal canal. The myenteric plexus is situated between the longitudinal and circular muscles. The submucous plexus lies in the submucosa. These plexuses are intimately connected with each other through numerous connecting rami. Postganglionic fibers derived from the prevertebral plexuses traverse the ganglia and contribute to the enteric plexuses. The preganglionic fibers to the enteric ganglia are components of the vagus and second and third or third and fourth sacral nerves. The enteric plexuses will be described in detail in Chapter IX.

Cephalic Sympathetic Plexuses.—The cephalic sympathetic plexuses may be regarded as an extension of the sympathetic trunk into the cephalic region. The superior cervical sympathetic ganglion gives rise to several internal carotid and several external carotid branches which constitute the internal and external carotid nerves respectively. The internal carotid branches become applied to the internal carotid artery as it enters the carotid canal in the temporal bone. As they continue cephalad they become separated into lateral and medial divisions. The lateral division gives rise to the *internal carotid* plexus which invests the internal carotid artery. The medial division gives rise to the *cavernous* plexus associated with the cavernous sinus. The external carotid branches join the plexus on the external carotid artery.

The Internal Carotid Plexus.—The internal carotid plexus sends communicating branches to the abducens nerve and semilunar ganglion. It also gives rise to the deep petrosal and carotico-tympanic nerves. The deep petrosal nerve joins the greater superficial petrosal to form the nerve of the pterygoid canal, which terminates in the sphenopalatine ganglion. The caroticotympanic nerves join the tympanic plexus.

The Cavernous Plexus.—The cavernous plexus sends communicating branches to the oculomotor, trochlear and ophthalmic nerves and the ciliary ganglion. It also supplies fibers to the hypophysis.

The Tympanic Plexus.—The tympanic plexus is formed mainly by the caroticotympanic nerves and a tympanic branch of the petrosal ganglion. It is situated on the medial wall of the middle ear and supplies fibers to the mucous membrane of the tympanum, mastoid cells and auditory tube. The tympanic plexus gives rise to a small branch, made up mainly of fibers which enter the plexus

through the tympanic branch from the petrosal ganglion, which unites with a branch from the genicular ganglion of the *nervus intermedius* to give rise to the lesser superficial petrosal nerve. This nerve passes through the temporal bone and joins the otic ganglion.

The External Carotid Plexus.—The external carotid plexus is made up of the external carotid branches of the superior cervical sympathetic ganglion. It accompanies the external carotid artery and gives rise to subordinate plexuses on the branches of this artery. It also supplies rami to the *glomus caroticum*. The subordinate plexuses on the middle meningeal and external maxillary arteries supply branches to the otic and submaxillary ganglia respectively.

The external carotid plexus is also continued downward on the common carotid artery as the *common carotid* plexus. Not uncommonly fibers arising in the middle and inferior cervical sympathetic ganglia join the common carotid plexus through which they may enter either the internal or the external carotid plexus and contribute to the sympathetic innervation of the head.

Cephalic Autonomic Ganglia.—The cephalic autonomic ganglia are situated in relation to the oculomotor nerve and the several divisions of the trigeminal nerve, but are related functionally to the nerves through which they receive preganglionic fibers.

The Ciliary Ganglion.—The ciliary ganglion is a small reddish ganglion located in the posterior portion of the orbit, between the lateral rectus muscle and the optic nerve, and in proximity to the ophthalmic artery. It is connected with the inferior division of the oculomotor nerve by a short *motor* root through which it receives preganglionic fibers, and with the nasociliary branch of the ophthalmic nerve by a long *sensory* root. It also receives a slender ramus, the *sympathetic* root, derived from the cavernous plexus on the internal carotid artery. This ramus may join the ciliary ganglion as an independent root or it may be incorporated in the long root from the nasociliary nerve. Twelve to fifteen slender rami, the *short ciliary* nerves, arise from the ciliary ganglion and, passing forward above and below the optic nerve, convey fibers to the eye, its extrinsic muscles and the blood vessels.

The Sphenopalatine Ganglion.—The sphenopalatine ganglion is a small reddish ganglion located deeply in the sphenopalatine fossa, close to the sphenopalatine foramen, and at the peripheral end of the nerve of the pterygoid canal, through which it receives both preganglionic (motor root) and sympathetic (sympathetic root) fibers. The preganglionic fibers are components of the facial nerve and are conveyed to the nerve of the pterygoid canal via the greater superficial petrosal nerve. The sympathetic fibers are derived from the plexus on the internal carotid artery and join the nerve of the pterygoid canal through the deep petrosal nerve. Branches of the

maxillary nerve join the sphenopalatine ganglion and constitute its sensory roots.

Sluder (1920) advanced certain clinical data which seem to indicate that the nerve of the pterygoid canal also conveys afferent impulses. He suggested the possibility that the sphenopalatine ganglion may include some ganglion cells which are essentially afferent. More recently Delie (1927), on the basis of his clinical findings, advanced the opinion that the sphenopalatine ganglion is not purely autonomic, but in part of vagus origin. He also maintained that the nerve of the pterygoid canal includes fibers of vagus origin which join the superior cervical sympathetic ganglion through the rami connecting this ganglion with the vagus nerve and continue upward in the internal carotid nerve. These findings await further anatomical confirmation.

Peripheral rami arising from the sphenopalatine ganglion are distributed as follows: A *pharyngeal* ramus, passing backward through the pharyngeal canal, supplies the mucous membrane of the roof of the pharynx. Three palatine nerves reach the palate through the palatine canals. The *anterior* or *great palatine* nerve gives rise to anterior filaments which reach the incisor teeth and communicate with branches of the naso-palatine nerve. In the palatine canal it gives rise to a small ramus, the *posterior inferior lateral nasal* nerve, which supplies the mucous membrane of the inferior concha. The *middle* or *external palatine* and *posterior* or *small palatine* nerves supply the mucous membrane of the soft palate, uvula and palatine tonsil. A small ramus, the *posterior superior lateral nasal* nerve supplies the mucous membrane of the middle and inferior choanæ. The *nasopalatine* nerve supplies the mucous membrane of the hard palate and the roof and septum of the nose. One or more *orbital* rami also pass upward from the sphenopalatine ganglion to the periosteum of the orbit.

The Otic Ganglion.—The otic ganglion is a small ganglion located medial to the mandibular nerve just below the foramen ovale and at the posterior border of the pterygoid muscle. Its preganglionic (motor root) fibers are components of the glossopharyngeal nerve and are conveyed to the ganglion via the lesser superficial petrosal nerve. This nerve also constitutes the sensory root of the otic ganglion. Its sympathetic root is derived from the plexus on the middle meningeal artery. Communicating rami arising from the otic ganglion join the nerve of the pterygoid canal, the auriculo-temporal nerve and the chorda tympani. It also sends peripheral rami to the tensor tympani and tensor veli palatini muscles.

The Submaxillary Ganglion.—The submaxillary ganglion is a small reddish ganglion located between the lingual nerve and the duct of the submaxillary gland. Its preganglionic (motor root) fibers are components of the facial nerve and join the lingual nerve via the

chorda tympani. Its sensory root, made up mainly of components of the nervus intermedius, joins the ganglion as a slender ramus of the lingual nerve. Its sympathetic root is derived from the plexus on the external maxillary artery. Peripheral rami arising from the submaxillary ganglion supply the submaxillary gland and its duct. Other peripheral fibers join the lingual nerve and are conveyed to the sublingual gland.

Small aggregates of sympathetic neurons occur between the intrinsic muscles in the posterior portion of the tongue. These may be designated as *lingual ganglia*. Most of them lie within the range of distribution of the glossopharyngeal nerve, through which they probably receive preganglionic fibers.

Other Ganglia Associated with the Cranial Autonomic Nerves.—Other ganglia which are intimately associated with the cranial autonomic nerves are the geniculate ganglion of the nervus intermedius, the petrosal ganglion of the glossopharyngeal and the jugular and nodose ganglia of the vagus nerve. These ganglia are regarded by some as in part autonomic (Coffey, Brown, and Humber, 1927). The *geniculate* ganglion is situated in the facial canal at the genu of the facial nerve. Three small nerves arise from this ganglion: (1) The greater superficial petrosal nerve contains chiefly preganglionic fibers to the sphenopalatine ganglion and sensory fibers which traverse this ganglion to be distributed through the middle and posterior palatine nerves to the mucous membrane of the soft palate. (2) The geniculotympanic nerve enters the tympanic plexus and, continuing through the latter, joins the small superficial petrosal nerve. (3) The external superficial petrosal nerve is an inconstant ramus which joins the sympathetic plexus on the middle meningeal artery. The *petrosal* ganglion is situated in the lower part of the jugular foramen. It receives a ramus from the superior cervical sympathetic ganglion and gives off a ramus which passes into the tympanic plexus and emerges as the small superficial petrosal nerve. The *jugular* and *nodose* ganglia of the vagus are intimately associated with the superior cervical sympathetic ganglion. Their connections with the latter ganglion are described above.

The theory that the ganglia of the vagus are in part autonomic is based on both histological and experimental findings. Müller (1911) and Möllgaard (1912) maintained, on the basis of their histological findings, that the nodose ganglion contains at least a few multipolar ganglion cells. On the basis of available histological and embryological data, Kidd (1914) advanced the opinion that the axons of neurons in the dorsal motor nucleus of the vagus effect synaptic connections with neurons in the nodose and possibly also in the jugular ganglion. More recently Hess and Pollak (1926) advanced experimental data which seem to indicate the existence

of autonomic neurons in the vagus ganglia. In preparations of the vagus ganglia of dogs which had been subjected to extirpation of the pancreas, and kept alive for three weeks by the administration of insulin as required, they observed degenerative changes in a goodly percentage of the ganglion cells in the jugular, and a smaller percentage in the nodose ganglion. Since no degenerative changes were observed in the dorsal motor nucleus of the vagus, they concluded that the nerve cells which underwent degeneration in the jugular and nodose ganglia represent parasympathetic neurons.

COMPOSITION AND STRUCTURE OF THE SYMPATHETIC TRUNKS.

Each sympathetic trunk consists essentially of a series of ganglia, the vertebral ganglia and the connecting internodal rami. The internodal rami consist primarily of visceral afferent and pre-ganglionic visceral efferent fibers which enter the sympathetic trunk through the white communicating rami. The preganglionic neurons are located in the intermediolateral cell column and adjacent parts of the gray matter throughout the thoracic and upper lumbar regions of the spinal cord. Their axons enter the sympathetic trunk via the white communicating rami and either terminate in one of its ganglia in synaptic relationship to sympathetic ganglion cells or traverse the trunk for a shorter or longer distance and continue peripherally in one of its branches to terminate in a sympathetic ganglion lying farther peripherally. The visceral afferent neurons which send fibers into the sympathetic trunk are components of the posterior nerve roots. The visceral afferent fibers enter the sympathetic trunk via the white rami and traverse it without making synaptic connections with sympathetic neurons. The internodal rami throughout the greater part of the sympathetic trunk also contain some fibers which arise from sympathetic ganglion cells and run longitudinally for a shorter or longer distance before entering the nerves through which they are conveyed to their peripheral destination.

The preganglionic and visceral afferent fibers which make up the cervical internodal rami enter the sympathetic trunk via the white communicating rami of the upper five or six thoracic nerves. Probably no visceral afferent fibers ascend in the cervical sympathetic trunk beyond the middle cervical ganglion (Ranson and Billingsley, 1918); consequently, the upper internodal ramus consists almost exclusively of preganglionic fibers which terminate in the superior cervical sympathetic ganglion. In sections of the sympathetic trunk taken just below the superior cervical ganglion, fascicles of unmyelinated fibers are not infrequently observed at the periphery of the internodal ramus. These fibers do not degenerate following

section of the trunk in the lower cervical levels. Obviously, they are postganglionic fibers which arise in the superior cervical ganglion and run in the internodal ramus for a short distance before entering a peripheral ramus of distribution. The possibility that some of these fibers may be the axons of commissural neurons is not precluded, but evidence that commissural neurons occur in the sympathetic trunk is wanting (Johnson, 1918, 1921). Exclusive of such inconstant peripheral fascicles of postganglionic fibers, nearly all the fibers in this portion of the sympathetic trunk are myelinated. They are of relatively small caliber and closely aggregated. In the cat the majority of these fibers, according to measurements carried out by Ranson and Billingsley (1918), vary from 1.5 to 3.5 microns in diameter. They found relatively few fibers with a diameter greater than 4.5 microns and occasional ones with a diameter of 6.5 or 7 microns. All these fibers undergo degeneration toward the superior cervical ganglion following section of the sympathetic trunk at any level in the neck.

After section of the communicating rami of the first and second thoracic nerves and the sympathetic trunk below the stellate ganglion, Langley (1896, 1900) found no intact myelinated fibers in the cervical sympathetic trunk. He concluded, therefore, that no myelinated fibers run from one of the cervical sympathetic ganglia to another or enter the sympathetic trunk through cervical communicating rami. Ranson and Billingsley (1918) concurred in this conclusion. That no preganglionic fibers pass through the superior cervical ganglion into the nerves arising from it is indicated by the absence of degenerated fibers in these nerves following degenerative section of the cervical sympathetic trunk, and the result of cervical sympathetic stimulation following paralysis of the superior cervical ganglion.

Langley also showed that stimulation of the sympathetic trunk in the cervical region elicits no general body reflexes. This would seem to indicate the absence of afferent fibers, at least of those mediating painful afferent impulses. Absence of afferent fibers in this portion of the sympathetic trunk is also indicated by the results of the histological studies of Ranson and Billingsley (1918).

Below the middle cervical ganglion or the origin of the middle cardiac nerve, the cervical sympathetic trunk contains both preganglionic and visceral afferent fibers. The majority of the latter are conveyed to their peripheral destination through the middle and inferior cardiac nerves and rami arising from the ansa subclavia to be distributed to the heart and lungs.

Throughout the thoracic and lumbar regions the sympathetic trunk contains both preganglionic and visceral afferent fibers. These fibers, the great majority of which are myelinated, are arranged in a compact bundle, usually oval in cross-section. Unmy-

elinated fibers occur only in small numbers above the fourth thoracic ganglion. Below this level they are more abundant and are arranged

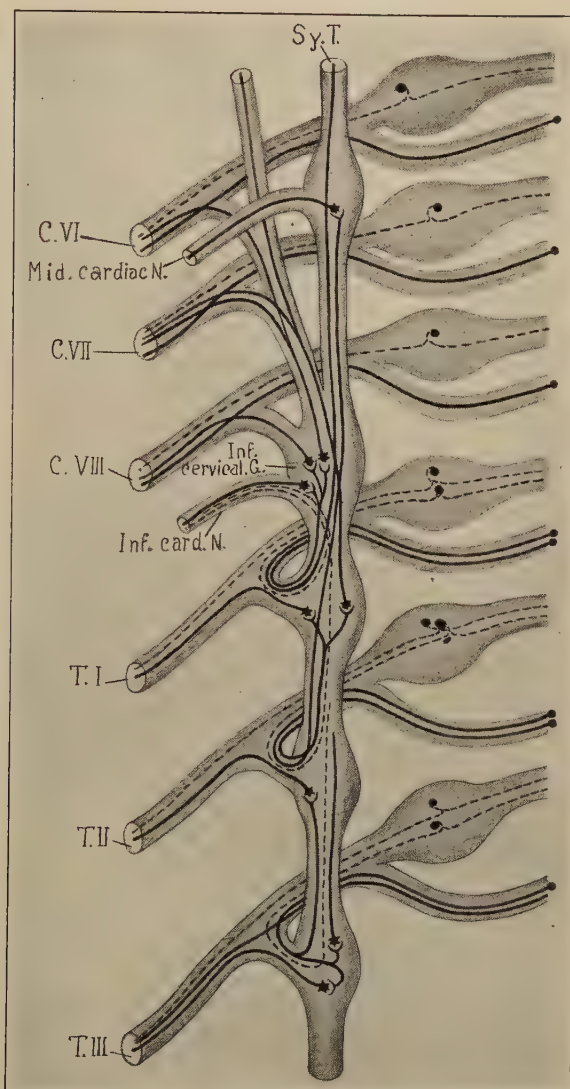


FIG. 8.—Diagram showing the arrangement of preganglionic and postganglionic efferent and visceral afferent fibers in the upper thoracic and lower cervical portions of the sympathetic trunk.

in a crescent-shaped fascicle at the periphery of the larger oval fascicle of myelinated fibers. This crescent-shaped fascicle also

contains unmyelinated fibers in about the same proportions as the gray rami communicantes. It is made up of fibers which arise in the ganglia of the sympathetic trunk and run longitudinally for a shorter or longer distance before entering a ramus of distribution (Ranson and Billingsley, 1918).

Above the sixth thoracic ganglion, the great majority of the fibers in the sympathetic trunk are ascending preganglionic fibers destined to terminate in the upper thoracic and cervical ganglia. The lowest source of preganglionic fibers to the superior cervical ganglion is the seventh thoracic nerve. Fibers which enter the sympathetic trunk through white rami as low as that of the ninth thoracic nerves are known to reach the inferior cervical ganglion. From the sixth to the ninth thoracic ganglion the sympathetic trunk contains both ascending and descending preganglionic fibers. Below the tenth thoracic ganglion it contains chiefly descending preganglionic fibers from the lower thoracic and lumbar nerves to the more caudal ganglia of the trunk and the splanchnic nerves. The highest source of preganglionic fibers which enter the splanchnic nerves is the fifth, possibly the fourth, thoracic nerve. Fibers which enter the sympathetic trunk through a given white ramus may be distributed to from five to ten successive ganglia, although any one preganglionic fiber probably does not give off branches to so large a number of ganglia. These statements regarding the distribution of preganglionic fibers are based on Langley's (1892, 1900, 1903) findings in the cat, which in general corroborate and extend Gaskell's (1886) earlier findings in the dog. Müller (1909) has shown that the sympathetic trunk in man exhibits a similar distribution of preganglionic fibers.

Ranson and Billingsley (1918) presented evidence which indicates that the visceral afferent components of the sympathetic trunk are chiefly myelinated fibers of large and medium size, but that small myelinated and unmyelinated visceral afferent fibers also occur. The latter are not easily distinguished from the preganglionic fibers. They pointed out that large and medium-sized myelinated fibers are present in varying numbers in different parts of the thoracic sympathetic trunk. Such fibers are relatively few above the sixth thoracic ganglion. They gradually increase in number below this level until the roots of the greater splanchnic nerve are reached, through which a large proportion of these fibers is conveyed to the viscera. Large and medium-sized myelinated fibers are present in relatively small numbers below the roots of the splanchnic nerves. Some of these fibers continue downward into the sacral region.

The unmyelinated fibers which enter the sympathetic trunk through white rami, according to Ranson and Billingsley, have

a distribution similar to that of the myelinated fibers which they regarded as sensory, and are arranged in bundles between the myelinated fibers in the oval fascicle. They occur only in small numbers in the upper thoracic segments, but are present in greater abundance in those segments of the sympathetic trunk in which the large and medium-sized myelinated fibers are more numerous. The possibility that some of these unmyelinated fibers are preganglionic fibers which have lost their myelin sheaths is not precluded by the data here presented, but Ranson and Billingsley (1918) showed, by degeneration experiments, that they are fibers which take origin from cells in the spinal ganglia.

In the sacral region the sympathetic trunk contains both myelinated and unmyelinated fibers. Here the crescent-shaped fascicle described in the thoracic region seems to be absent, but the unmyelinated fibers run in bundles among the myelinated fibers. The great majority of these fibers are descending components of the lower thoracic and upper lumbar nerves (Johnson, 1921). They include both preganglionic and visceral afferent fibers. According to Johnson, large myelinated fibers also enter the sacral sympathetic trunk through the gray rami of the lower lumbar and sacral nerves. He was able to demonstrate, by degeneration experiments, that these are dorsal root fibers and, therefore, afferent in character. The possibility that dorsal root fibers may enter the sympathetic trunk through gray rami was pointed out by Langley (1896), but he did not anticipate that they do so in such large numbers as Johnson's observations seem to indicate.

In a recent experimental anatomical study Kuntz and Farnsworth (1928) found that nearly all the myelinated fibers in the gray rami of the sixth and seventh lumbar and first sacral nerves in the dog underwent degeneration following section of the sympathetic trunk just above the level of the gray ramus joining the sixth lumbar nerve. Similar results were observed following section of both roots of the upper five lumbar nerves distal to the spinal ganglion, leaving the sympathetic trunk intact. The myelinated fibers in the gray rami of the lower lumbar and sacral nerves which underwent degeneration under these conditions must be regarded as components of the dorsal roots of the lower thoracic and upper lumbar nerves which enter the sympathetic trunk through the white rami of these nerves and join the lumbosacral plexus through the gray rami of the lower lumbar and sacral nerves. According to these findings, the majority of the large myelinated fibers in the gray rami of the lower lumbar and upper sacral nerves, in the dog, must be regarded, not as dorsal root components which enter the sacral sympathetic trunk through these gray rami, but as dorsal root components which join the lower lumbar and sacral nerves from the sympathetic trunk.

In an experimental study of the distribution of fibers of spinal origin in the sympathetic trunks by means of the degeneration method, Matsui (1925) observed, following section of the roots of one or more thoracic nerves in the dog, that in some instances a small number of fibers also underwent degeneration in the sympathetic trunk on the unoperated side. He concluded, therefore, that preganglionic fibers which enter the sympathetic trunk on one side, in some instances, cross over in small numbers and enter the sympathetic trunk on the opposite side. The paths through which such fibers reach the opposite sympathetic trunk were not determined. They probably traverse the rami which connect the sympathetic trunks.

RATIO OF PREGANGLIONIC TO POSTGANGLIONIC NEURONS.

Casual study of the autonomic system would lead one to conclude that the neurons in the autonomic ganglia far outnumber the preganglionic fibers. This probably is true with regard to all autonomic ganglia. Consequently, a single preganglionic fiber must make synaptic connections with more than one postganglionic neuron. Extensive data bearing on this point are not available; however, Billingsley and Ranson (1918) have given us valuable information regarding the ratio of the preganglionic fibers in the upper internodal ramus of the sympathetic trunk to the neurons in the superior cervical sympathetic ganglion. By carefully executed actual counts, this ratio was determined to be approximately 1 to 32. It does not follow that this ratio obtains throughout the autonomic nervous system. Neither does it follow that a single preganglionic fiber actually makes synaptic connections with approximately thirty-two neurons in the superior cervical ganglion. The possibility of intraganglionic commissural neurons is not precluded, although strong evidence has been advanced against the occurrence of either inter- or intraganglionic commissural neurons in the sympathetic trunk. Lawrentjew (1924) described fiber terminations in the form of pericellular apparatuses on neurons in the superior cervical ganglion in the cat, which remained intact eight to thirty days after isolation of the ganglion by section of all its rami, including the upper internodal ramus of the sympathetic trunk. He interpreted these structures as the terminations of collaterals arising from the axons of neurons within the superior cervical ganglion. Similar pericellular apparatuses were observed by Lawrentjew in preparations of the superior mesenteric ganglion nine to fifteen days after section of all its afferent connections. Pines (1927) also described the terminations of collaterals arising

near the base of the axon of one neuron on the cell body of a neighboring neuron in the ciliary ganglion in man. In view of all the evidence to the contrary, these findings cannot be accepted without further confirmation. If the intraganglionic connections described by Lawrentjew and Pines actually exist, it is unnecessary to assume that preganglionic fibers make direct synaptic connections with all the autonomic neurons. On the other hand, it is not unreasonable to assume that a single preganglionic fiber may make direct synaptic connections with thirty-two or more postganglionic neurons.

Not a few investigators have pointed out intimate relationships of adjacent sympathetic neurons brought about through their dendrites. The dendrites of adjacent neurons sometimes interlace with each other to form a glomerular structure. Sometimes dendrites of one neuron form a pericellular network around the cell body of a neighboring neuron. Such dendritic relationships have been regarded by some as accidental. Greving (1921), who studied them intensively, regarded it as highly probable that impulses may pass from one autonomic neuron to another through such dendritic connections.

To what extent preganglionic fibers give off collaterals in ganglia through which they pass en route to the one in which they terminate is not known with certainty. This question is discussed by Billingsley and Ranson (1918) with reference to the preganglionic fibers to the superior cervical ganglion. By stimulation of the upper thoracic nerves in the cat within the spinal canal, Langley (1892) showed that the preganglionic fibers for the dilatation of the pupil are components of the first three; those for the innervation of the nictitating membrane, submaxillary gland and bloodvessels of the head, of the first five; those for the innervation of the hair of the face and neck, of the first seven thoracic nerves. The preganglionic fibers to the middle and inferior cervical ganglia for acceleration of the heart are components of the second to the fifth thoracic nerves. Pilomotor, secretory and vasomotor preganglionic fibers to the inferior cervical ganglion arise from the fourth to the ninth thoracic nerves.

The preganglionic fibers contained in the first three thoracic nerves, excepting the accelerator fibers, apparently make synaptic connections only in the superior cervical ganglion. Probably, no preganglionic fibers arising from the first three thoracic nerves give off collaterals in the inferior or middle cervical ganglion and continue on to the superior cervical ganglion. Many fibers from the fourth and fifth thoracic nerves terminate in both the superior and inferior cervical ganglia. A few fibers from the sixth and seventh thoracic nerves also terminate in the superior cervical ganglion. To what extent any of these fibers make synaptic connections in the inferior

cervical ganglion is uncertain. It must be remembered in this connection that most of the functions subserved through the superior cervical ganglion, *e. g.*, dilatation of the pupil, salivation and lacrimation, are highly specialized. It is quite improbable that preganglionic fibers subserving these functions give off collaterals in the inferior cervical and upper thoracic ganglia, through which quite a different set of functions is subserved. On the other hand, it is quite probable that preganglionic fibers arising from the fourth to the ninth thoracic nerves, which subserve vasomotor and pilomotor functions, make synaptic connections in both the inferior and superior cervical ganglia.

CHAPTER II.

THE AUTONOMIC GANGLION CELLS.

GENERAL MORPHOLOGY.

THE neurons in the autonomic nervous system are, in general, aggregated in ganglia which are more or less definitely delimited and enclosed in a connective tissue capsule. The cell bodies of the neurons in all the larger ganglia are enclosed in delicate cell capsules which are made up of a layer of small endothelial cells and a non-cellular membrane with which the endothelial cells lie in intimate contact. The cell capsules are usually separated by a small amount of interstitial connective tissue, although in sections they may appear to lie in close proximity to each other. The interstitial connective tissue is continuous with the connective tissue capsule of the ganglion. It is present throughout the ganglion, and the intraganglionic blood vessels are imbedded in it. Slit-like lymph spaces which are connected with other lymph spaces in the ganglion also occur in close proximity to the cell capsule (Key and Retzins, 1876). The relationship of the lymph spaces to the cell capsule suggests that the endothelial cells lining the capsules play an important rôle in the metabolic interchange of materials and degenerative processes involving the ganglion cells. Many of the smaller terminal ganglia, *e. g.*, those in the walls of the alimentary canal, are less sharply delimited. They are surrounded by connective tissue, but a definitive ganglionic capsule is not apparent in all cases. Neither are the ganglion cells in the enteric ganglia enclosed in cell capsules. The bundles of nerve fibers which enter the autonomic ganglia run a more or less regular course within the ganglion in some instances, but exhibit no regularity within the ganglion in others. Not uncommonly they interlace with each other in a more or less complex manner. These fiber bundles separate the ganglion cells into groups of various sizes and forms. In some instances, as observed in sections of the ganglion, the ganglion cells appear to be arranged in more or less definite cell columns; in others, they appear to be arranged in irregular groups. The terminal branches of fibers of extrinsic origin which terminate in a given ganglion ramify among the ganglion cells and form an intercellular plexus of fine fibers. Many of the dendrites of the ganglion cells also penetrate the cell capsules and ramify more or less widely, but do not, in most instances, extend beyond the borders of the ganglion. Many of the shorter dendrites do not penetrate the cell capsule (Fig. 9).

In mammals the neurons in the autonomic ganglia are mainly multipolar cells. Bipolar and unipolar neurons have recently been described in the ciliary ganglion in man (Pines, 1927), although the great majority of neurons in this ganglion are multipolar. The

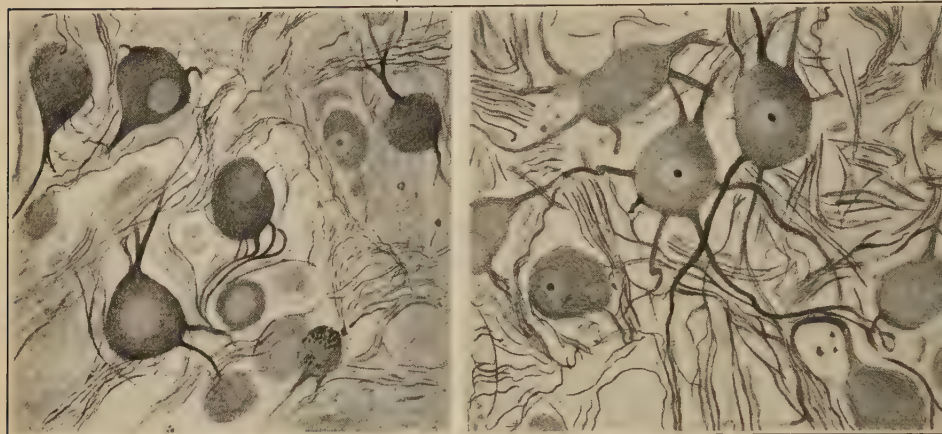


FIG. 9.—Ganglion cells (human). *A*, From thoracic sympathetic trunk. *B*, From celiac ganglion (pyridine silver).

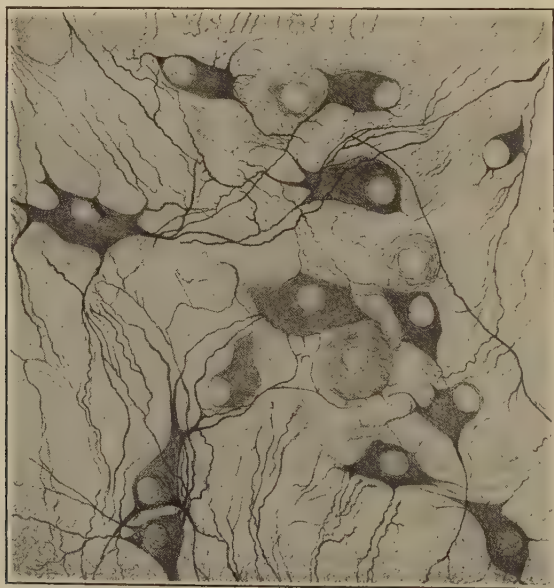


FIG. 10.—Ganglion cells of the myenteric plexus as observed in a tangential section of the intestine of the dog (pyridine silver).

autonomic neurons exhibit a wide range in size and form. In the vertebral and prevertebral ganglia the majority of the cell bodies are somewhat angular, but not definitely elongated (Fig. 9). In the walls of the visceral organs, *e. g.*, the gastro-intestinal canal, many of the ganglion cells are definitely elongated and flattened (Fig. 10). As observed in tangential sections of the stomach and intestine, many of the flattened ganglion cells in the myenteric plexus exhibit a more or less irregular, angular outline, with one axis considerably longer than the other. In the ganglia of the submucous plexus the ganglion cells exhibit less variation in form and are arranged more compactly. In general, the location and form of the ganglion must be regarded as a factor in determining the form of the ganglion cell. According to Spiegel and Adolf (1922), the greatest diameter of the majority of the neurons in the autonomic ganglia in man falls within a range of 35 to 45 microns, although many of the smaller neurons exhibit a maximum diameter of only 20 to 25 microns. They also observed occasional large spindle-shaped ganglion cells, in preparation of human material, whose long axis measured 50 to 60 microns.

In birds the majority of the neurons in the autonomic ganglia are also multipolar cells. In general, they are similar in form and structure to the autonomic ganglion cells in mammals. According to certain investigators (von Lenhossek, 1911; Carpenter, 1911), the ciliary ganglion in birds contains only unipolar ganglion cells. Ganglion cells of the multipolar type also seem to predominate in the autonomic ganglia in reptiles. In the turtle Huber (1899) observed multipolar neurons in all the ganglia examined, although both bipolar and unipolar neurons also occur in these ganglia. According to von Lenhossek (1911), the ciliary ganglion in reptiles contains only unipolar ganglion cells. Neurons of the unipolar type also predominate in the autonomic ganglia in the Amphibia. According to Smirnow (1900), multipolar neurons occur in small numbers in the ganglia of the sympathetic trunks in these animals. Huber (1899) and Nemiloff (1901) found only multipolar neurons in certain of the peripheral ganglia, especially those in the myenteric and submucous plexuses, in the Amphibia. In the fishes the majority of the autonomic neurons are multipolar, although bipolar and unipolar neurons also occur in the autonomic ganglia in these animals.

INTERNAL STRUCTURE.

Neurofibrils.—Neurofibrils are constant constituents of autonomic ganglion cells. They are commonly present throughout the cytoplasm, including the axon and dendrites, but exhibit a wide range of variation in abundance, distribution and configuration. Preparations of ganglia in which neurofibrils are well stained and

abundant in the majority of the ganglion cells commonly reveal some cells in which neurofibrils may be observed only in the cell processes and the peripheral portions of the cell body, but not in the perinuclear zone. The neurofibrils in such cells also appear to be more delicate than those in which the neurofibrillar structure is more abundant. In many of the ganglion cells they seem to run singly or in small bundles through the cell body in various directions (Fig. 11); in others they appear to interlace with each other in

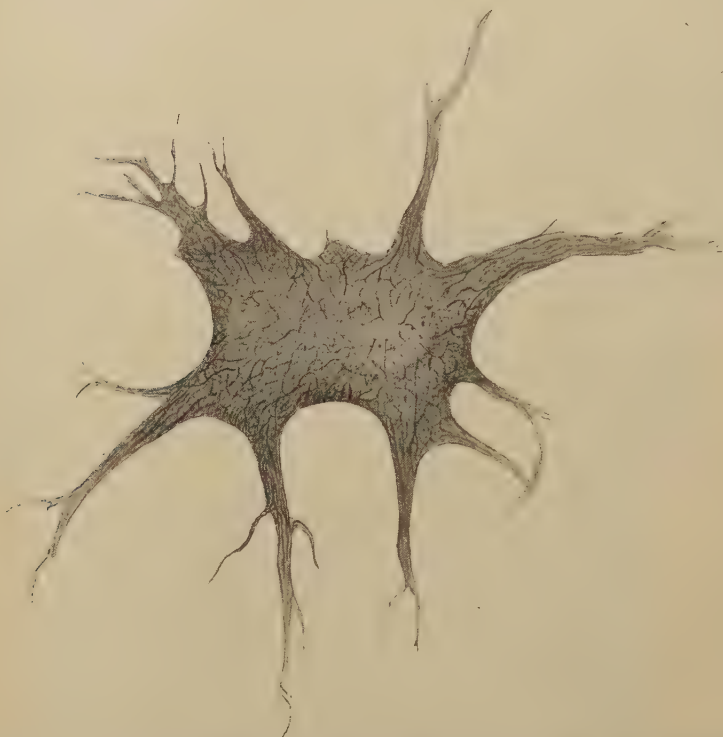


FIG. 11.—Sympathetic ganglion cell (dog) drawn from a pyridine silver preparation to illustrate neurofibrillar structure.

a more or less complex manner, the deeper fibrils forming a perinuclear plexus. In general, the neurofibrils in the deeper layers of the cytoplasm seem to be arranged with reference to the nucleus; those in the superficial layers with reference to the dendritic processes and the periphery of the cell body. In many instances the deep and superficial complexes of neurofibrils are quite distinct in their arrangement, but not independent of each other. Cajal (1905) recognized these two neurofibrillar configurations and described a

peripheral and a perinuclear neurofibrillar network. The perinuclear arrangement of neurofibrils has recently been emphasized by Tiegs both in the motor neurons in the spinal cord (1926) and the ganglion cells in the sympathetic trunks and enteric plexuses (1927). He advanced the theory that the perinuclear plexus of neurofibrils is involved in the neuron junction and constitutes the seat of functional integration. In preparations in which the neurofibrillar structure is well differentiated, neurofibrils lying parallel with each other may be observed in the cell processes throughout the greater part of their extent.

According to Cajal (1905) and Laignel-Lavastine (1906), the neurofibrillar substance in the majority of the autonomic ganglion cells in mammals comprises a perinuclear network which is fairly compact and a peripheral network which is less compact. Interlacing or anastomosing fibrils connecting these two networks are usually not apparent. Michailow (1908) attempted to classify the autonomic ganglion cells in mammals on the basis of their neurofibrillar structure. He recognized a perinuclear and a peripheral neurofibrillar network in certain of these cells, but pointed out that in others in which a real neurofibrillar network is present, it is not differentiated into a perinuclear and a peripheral portion. In some of these cells, according to his observations, the perinuclear zone seems to be quite devoid of neurofibrils. Michailow's classification includes some sixteen ganglion cell types with as many different configurations of their neurofibrils. We do not regard this classification as important. It should be pointed out, however, that Michailow recognized, in many of the autonomic ganglion cells, a neurofibrillar structure in which the fibrils neither anastomose nor give rise to branches, but ramify throughout the entire cell body and extend out into the axon and dendritic processes. Individual neurofibrils may, in many instances, be traced from a dendritic process or from the axon into the cell body where they conform to some particular configuration pattern. Individual neurofibrils can rarely, if ever, be traced from one cell process through the cell body and into another cell process.

Definite knowledge regarding the finer structure or composition of the neurofibrils is wanting. None of the methods available at present seems adequate for the study of their constituent elements. That they are not homogeneous in their structure is quite evident. As pointed out by Michailow, they exhibit a wide range of variation in configuration. They also vary in caliber and other recognizable characters. Such variations, doubtless, are significant, although no important conclusions can be based on our present knowledge regarding them. Michailow expressed the opinion that the large caliber of the neurofibrils in some of the autonomic ganglion cells represents hypertrophy and may have pathological significance.

Chromidial Substance.—Chromidial substance is a common constituent of the autonomic ganglion cell body. As observed in some cells it is distributed quite uniformly throughout the cytoplasm of the cell body and the proximal parts of the dendrites; in others it is aggregated either in the peripheral or perinuclear zone. Intergradations between fairly uniform distribution and aggregation either in the peripheral or perinuclear zone are not uncommon. The variations in the quantity of the chromidial substance and its distribution are closely correlated with the functional states of the cells. In general, the chromidial bodies near the periphery of the cell body are larger than those in the deeper layers of the cytoplasm.

Chromidial substance appears relatively early in the ganglion cells throughout the autonomic nervous system. It is fairly abundant in these cells in man even before birth. In the newborn the chromidial substance in the autonomic ganglion cells exhibit practically the same range of variation in the size and distribution of the chromidial bodies as in the adult (Spiegel and Adolf, 1922).

According to Ping (1921), who gave especial attention to the development and distribution of the chromidial bodies in the largest cells in the superior cervical sympathetic ganglion of the albino rat from birth to maturity, these cells exhibit progressive changes in the quantity of the chromidial substance and in the character and distribution of the chromidial bodies. During the first twenty days of postnatal life the chromidial substance is still fairly uniformly distributed throughout the cytoplasm and the chromidial bodies are still relatively small, but before the close of this period a beginning of aggregation of the chromidial granules is apparent in some of the cells. Following this period, the chromidial bodies in the cells in question become larger and stain more intensely. Before the sixtieth day of postnatal life the chromidial substance in the majority of these cells is aggregated either in the peripheral or perinuclear zone. Many of them also exhibit the same modes of distribution of the chromidial substance following this period. In view of the effect of cellular activity on the abundance and distribution of the chromidial substance in ganglion cells, it is not improbable that the variations which Ping described as correlated with age, may be, in a large measure, expressions of the metabolic states of the cells and only indirectly dependent on age.

The chromidial substance in the autonomic ganglion cells is affected by cell activity and fatigue in essentially the same manner as that in the neurons in the cerebrospinal nervous system. Vas (1892) observed enlargement of the cells and displacement of the chromidial substance toward the periphery in the cervical sympathetic ganglia following stimulation for fifteen minutes. Lambert (1893) observed similar aggregation of the chromidial substance in

the peripheral zone following stimulation, but no changes in the size of the ganglion cells. Mann (1894) observed enlargement of autonomic ganglion cells during cell activity and shrinking both of the nucleus and cytoplasm as the cells become fatigued. He also maintained that the chromidial bodies become enlarged during

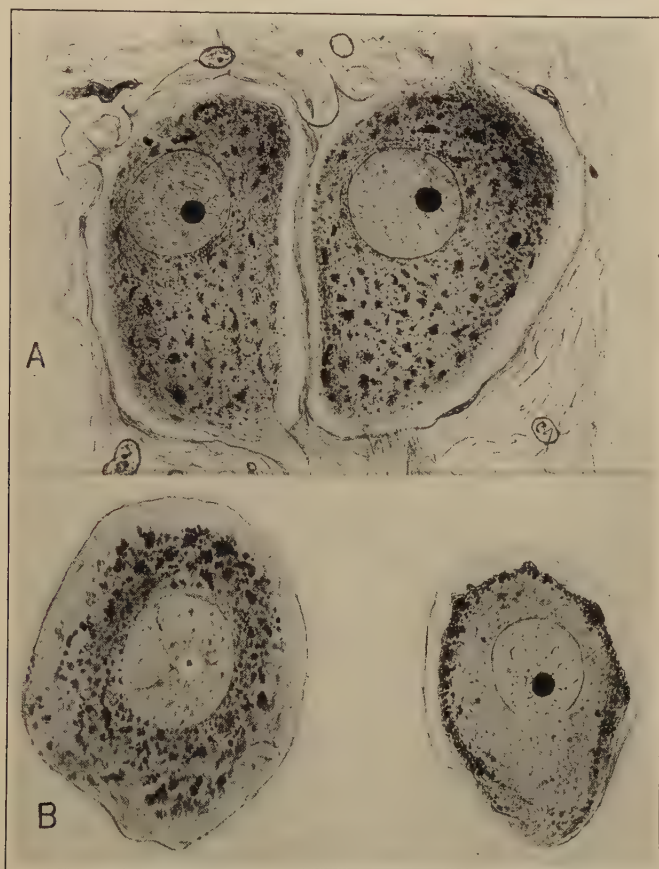


FIG. 12.—Sympathetic ganglion cells (cat). *A*, Selected to illustrate normal distribution of chromidial substance in resting cells. *B*, Selected to illustrate variations in the distribution of the chromidial substance.

moderate cell activity, but prolonged stimulation results in diminution in the quantity of the chromidial substance. Lugaro (1895) also reported an initial enlargement of both the cell body and nucleus of autonomic ganglion cells due to cell activity. According to his observations, if these cells are subjected to prolonged stimulation, the enlargement of the cell body reaches its maximum in

five minutes, and that of the nucleus in thirty minutes. After this, both the cell body and the nucleus undergo diminution in size rapidly during the first few hours, and then more slowly. He also maintained that the chromidial substance was increased during the early phases and diminished during the later phases of cell activity. As the cells became fatigued they also exhibited a more diffuse distribution of the chromidial substance. Section of the preganglionic fibers to the superior cervical sympathetic ganglion (cat, rabbit), according to Sternsheim (1923), resulted in changes in the chromidial substance and diminution in the size of the neurons in this ganglion. The chromidial bodies became larger and more compactly aggregated and assumed a somewhat fibrous appearance. They also reacted more intensely to basic stains. The progressive changes in the chromidial content of the autonomic ganglion cells during stimulation and depression have not been studied systematically. Work now in progress in these laboratories strongly suggests that the changes are comparable to the progressive changes in the chromidial substance described by Dolley (see Chapter XVI) in certain neurons in the central nervous system, particularly the Purkinje cells in the cerebellum, during stimulation and depression.

Nucleus.—The nucleus in the autonomic ganglion cells is in general similar in appearance to the nucleus in the neurons in the central nervous system. It is usually relatively large, rounded or oval in outline and contains relatively little stainable material except one or more nucleoli. In the majority of the cells the nucleus is centrally located, but in many cells it occupies an eccentric position. In favorable preparations the nucleus exhibits a reticular structure and is separated from the cytoplasm by a distinct nuclear membrane.

The great majority of the neurons in the autonomic ganglia contain a single nucleus, but binuclear autonomic neurons are not uncommon, especially in rodents. Multinuclear autonomic neurons have also been reported. In man, according to Müller (1909), binuclear autonomic neurons occur only rarely. According to Spiegel and Adolf (1920), binuclear neurons are not uncommon in the autonomic ganglia, especially in young persons. They also reported the occurrence of multinuclear autonomic neurons in the newborn. According to their findings in human material, the binuclear autonomic neurons diminish in number with advancing age. They still found binuclear neurons in nearly every section of some of their material obtained from middle-aged persons, but rarely found any binuclear neurons in preparations of material obtained from aged persons. The observation that binuclear neurons occur quite commonly in the autonomic ganglia in young persons, but only rarely in the aged, led Spiegel and Adolf to advance the opinion that the binuclear cells retain the capacity to

undergo division without further nuclear changes, and that such division of some of these cells occurs even during adult life. Like Laignel-Lavastine (1906), they regarded the binuclear autonomic ganglion cells as reserve cells. The occasional occurrence of two autonomic neurons in a common cell capsule also lends support to the theory that binuclear cells may actually undergo division.

As stated above, binuclear autonomic neurons seem to be especially abundant in rodents. They are less abundant in these animals in the autonomic ganglia associated with the cranial nerves than in the ganglia of the sympathetic trunks and prevertebral plexuses. According to Apolant (1896), binuclear neurons occur only rarely in the cranial autonomic ganglia in rodents. Carpenter and Conel (1914) corroborated this observation and stated further that they found no binuclear neurons in the enteric plexuses in the rodents studied (rabbit, guinea-pig, muskrat, porcupine). They suggested that the common occurrence of binuclear neurons in the sympathetic ganglia and their relative infrequency or absence in the parasympathetic ganglia, in rodents, might be regarded as morphological evidence in favor of Langley's subdivision of the autonomic nervous system into the sympathetic and parasympathetic systems. A comparable distribution of binuclear and uninuclear autonomic neurons has not been observed in other groups of mammals.

Nucleus-plasma Ratio.—By careful measurements, Spiegel and Adolf (1922) found that the nuclei of the larger ganglion cells in the autonomic ganglia in man have a diameter of 12 to 13 microns, while those of the smaller ganglion cells have a diameter of 8 to 12 microns. The ganglion cell bodies, excluding those which are definitely elongated, have a diameter of 20 to 45 microns. In young children, according to their observations, the nuclei of the autonomic ganglion cells are nearly uniform in size, regardless of the size of the cell body. According to these findings, the nuclei of the smaller ganglion cells are larger in proportion to the size of the cell body than are the nuclei of the larger ones. Apparently, the nucleus increases in volume less rapidly than the cytoplasm during the growth of the largest cells in the superior cervical sympathetic ganglion in rats. According to Ping (1921), the nucleus-plasma ratio of these cells is 1 to 4 in the albino and 1 to 5 in the Norway rat at birth, and 1 to 12 in both varieties at maturity.

The nucleus-plasma ratio probably is fairly constant in mature autonomic ganglion cells of approximately uniform size. When all the neurons in a given ganglion are considered, the nucleus-plasma ratio seems to vary within relatively wide limits. These cells apparently do not conform closely to Hertwig's law of the constancy of the nucleus-plasma ratio. Heidenhain (1907) expressed the opinion that this may be due to the fact that neuroblasts have

the capacity to produce a short or long axon, according to their location and relationships to the tissues innervated by them. The apparent inconstancy in the nucleus-plasma ratio is especially striking in the autonomic ganglion cells, even though the cell processes are disregarded. In view of the apparent inconstancy of the nucleus-plasma ratio in the autonomic ganglion cells, the quantity of chromidial substance present in the cytoplasm is significant. This substance, being histo-chemically related to the chromatin in the nucleus, probably is, as Heidenhain suggested, present in relatively greater quantity in the larger than in the small cells, especially if the larger cells have long axons. Accordingly, he expressed the opinion that the nucleus-plasma ratio might still be regarded as constant on this basis.

Axon.—The axon of the autonomic ganglion cell commonly arises from an implantation cone, or axon hillock, which, as in the neurons in the central nervous system, is free from chromidial substance, but is less conspicuous in the former than in the latter cells. Neurofibrils may be traced through the implantation cone into the axon, where, in general, they lie closely aggregated and parallel to each other. In the majority of the autonomic neurons the axon is a slender unmyelinated fiber; however, myelinated axons are not uncommon in the autonomic nervous system. Autonomic fibers clothed by a very thin myelin sheath throughout at least a portion of their length occur throughout the autonomic nervous system. The nucleated neurilemma of the unmyelinated autonomic fibers lies in intimate contact with the fiber. Even in the case of those fibers which are covered by a thin layer of myelin, the neurilemma invests the axon so closely that nodes and incisures are not usually apparent. In mammals autonomic nerve fibers are rarely myelinated throughout their entire length. Those which are invested by myelin acquire their myelin sheath at unequal distances from their origin. Myelinated autonomic fibers are more abundant in proportion to the unmyelinated fibers in some parts of the body than in others. The ratio of myelinated to unmyelinated autonomic fibers also varies in the different classes of vertebrates and in different species in the same class. The data available at present do not warrant a definite conclusion regarding the ratio of myelinated to unmyelinated autonomic fibers in any vertebrate group. The sympathetic fibers which join the spinal nerves via the gray communicating rami, especially in mammals, are probably myelinated in greater proportion than those which supply the visceral organs, although myelinated fibers also exist among those arising from the prevertebral sympathetic ganglia. According to Huber (1913), the axons of the neurons in the ciliary ganglion are quite generally myelinated. In birds, according to Langley (1896), true gray communicating rami do not occur, but the axons of all the neurons in

the ganglia of the sympathetic trunks are myelinated. Myelinated autonomic nerve fibers have also been described in the Amphibia. Most of the accounts of the autonomic nerves in fishes and reptiles refer only to unmyelinated fibers. Myelinated autonomic fibers probably occur also in these classes of vertebrates. The data available at present do not warrant any conclusion regarding the significance of myelin sheaths in the autonomic nervous system. Neither do they indicate that the myelinated autonomic fibers differ functionally from those without a myelin sheath.

Since the great majority of the autonomic ganglion cells are post-ganglionic neurons in visceral efferent chains, their axons terminate in relation to the tissue elements innervated by them, viz.: muscle and gland cells. Individual axons can rarely be traced from their origin to their termination. Occasional observations are recorded, however, in which the axon of an autonomic neuron situated in proximity to the tissue innervated was traced without interruption throughout its entire extent.

The autonomic fibers supplying smooth muscle commonly form plexuses around the fasciculi. Fine fibers arising from these plexuses pass into the fasciculi, either singly or in small bundles, and, in general, run parallel to the muscle fibers, in relation to which they terminate by means of delicate terminal branches. These terminal branches, as described by various investigators, end on the smooth muscle cells in one or two terminal nodules. Hoffman (1907) regarded these terminal nodules as artifacts, and advanced the opinion that an end plexus exists which is composed of fibrils which give rise to loops which come into relation to the muscle cells, but the nerve fibrils go on without interruption. Michailow (1908) also supported the theory of an end plexus. He also described free terminations which, in favorable preparations, show ring-like and net-like fibrillar structures. He maintained that the neurofibrils are everywhere continuous, although free fiber terminations occur.

The autonomic fibers supplying the cardiac muscle also form plexuses around the fasciculi, from which fibers arise which penetrate the fasciculi and in general run parallel to the muscle fibers. Delicate branches of these fibers terminate on the cardiac muscle fibers in one, two or several nodular enlargements.

The sympathetic fibers which terminate in relation to skeletal muscles also exhibit delicate end rings or loops and end nets which resemble very closely the terminations of autonomic fibers on smooth muscle. These terminations, according to Boeke (1913), are hypolemmal in position and rest on granular sole plates, through which the fine reticular network in the sarcoplasm comes into relation with the neurofibrils. The majority of the investigators who have described the terminations of sympathetic fibers in skeletal muscles in general corroborated Boeke's description.

The autonomic fibers which terminate in relation to glands, according to most observers, form a plexus situated external to the *membrana propria*, from which fibers arise which penetrate the *membrana propria* and terminate in relation to the gland cells. Such terminations are always delicate, but exhibit a wide range of complexity and configuration.

Dendrites.—The autonomic ganglion cells vary widely in the number and morphological characters of their dendrites. The dendrites represent extensions of the cell body. They are usually broad at the base and taper distally. They commonly give rise to branches and frequently exhibit varicosities and other irregularities. They also contain neurofibrils which, in favorable preparations, may be traced far into their terminal branches. Chromidial bodies also occur in the broader proximal portions of the dendrites. Short dendrites may lie wholly within the cell capsule. The longer dendrites usually penetrate the cell capsule and ramify more or less widely within the ganglion. In some instances they extend beyond the borders of the ganglion in the fiber bundles associated with it.

Tiegs (1927) recently advanced the theory that the growth of dendrites in the autonomic ganglion cells, as in other multipolar neurons, is stimulated by the growth of axon collaterals into the cell body either singly or in bundles during embryonic life. According to this theory, the dendrites represent that portion of the cytoplasm which grows outward from the cell to envelop the fibrils that have grown into the cell. In connection with his studies of the neuron junctions, which he described as involving axon collaterals which actually penetrate the cell body and form a fibrillar plexus in the perinuclear zone, he pointed out that in reduced silver preparations in which the neurofibrils are brought out clearly, as well as in good methylene-blue preparations, the dendrites are usually short and give rise to few branches, but the dendrites of the same cells, examined in Golgi preparations, appear to be of enormous length. He explained this discrepancy on the basis of the impossibility of distinguishing between the dendrites and the axon collaterals which have grown into the cell, in Golgi preparations. If Tiegs' findings regarding the physical character of the neuron junction are corroborated by the results of further investigations, they will aid materially in explaining the origin and distribution as well as the function of dendrites.

The character and distribution of the dendrites were used by Dogiel as criteria for a classification of the autonomic neurons. In his early work (1896) he described three types which he regarded as distinct from each other. His first type included neurons with many short branching dendrites which he regarded as efferent in function. His second type included neurons with relatively few long dendrites which branch only sparingly for some distance from

the cell body, but give rise to several slender terminal branches which extend beyond the boundaries of the respective ganglia. These he regarded as sensory in function. In his third type he included certain neurons with long slender dendrites which do not extend beyond the borders of the respective ganglia, but ramify widely in the intercellular plexus. Cajal (1905) also described autonomic neurons of three types according to the character and distribution of their dendrites. In his first type he included neurons with long branching dendrites which radiate from the cell body in all directions. His second type consisted of neurons with long branching dendrites which arise from one side of the cell body and interlace with similar dendrites of a neighboring neuron to form a glomerulus. Michailow (1911) described nine distinct types of autonomic neurons according to the character and distribution of their dendrites. More recently Pines (1927) described not less than eight ganglion cell types in the ciliary ganglion in man, although his classification is not based solely on the character and distribution of the dendrites. Müller (1924) recognized the three ganglion cell types described by Cajal, but pointed out that many neurons in the autonomic ganglia do not conform to any of these types. All these attempts to classify autonomic neurons according to morphological types only emphasize the variability, especially of their dendritic processes, and add little to our knowledge of the functional relationships of the cells.

In addition to the glomerular structures formed by the interlacing dendrites of neighboring neurons, Cajal (1905) also described dendrites which terminate in a pericellular network on the cell body of a neighboring ganglion cell. Similar relationships of dendrites of autonomic neurons, especially in the superior cervical sympathetic ganglion, were also described by Müller (1909). E. Müller (1921) described the enteric plexuses in mammals as consisting in part of nerve nets composed of cells whose processes anastomose freely. Cole (1921) described anastomoses between cells in the myenteric plexus in the frog which, according to his observations, involve only the dendrites and connect relatively few cells. He observed no groups including more than four neurons. Neither did he find two such groups connected with each other. Neither Kuntz (1922) nor Johnson (1925) were able to find anastomoses between neurons in the enteric plexuses in mammals. Furthermore, Johnson has shown very clearly that the cells which E. Müller described as constituting a syncytial nerve net in the intestinal wall in mammals probably are not neurons, but connective-tissue cells.

In pyridine silver preparations of the small intestine of the dog, Waddell (1928), working under my supervision, occasionally observed two ganglion cells in the myenteric plexus joined together by a single large fiber. In some instances, the cells joined in this

manner lay in proximity to each other; in others, they were removed from each other by a distance equal to several times the diameter of a ganglion cell body. In no instance did he observe more than two ganglion cells joined together. We have confirmed these observations in the same material and also in preparations of the celiac ganglia in man. In view of all the data available, the existence in the mammalian autonomic nervous system of ganglion cells which anastomose with each other cannot be denied, yet this morphological relationship of ganglion cells to each other must be relatively uncommon. Neither have we any knowledge at present regarding the possible functional significance of such a relationship. Cole advanced the opinion that binuclear nerve cells and the anastomosing nerve cells which he observed in the frog belong to the same category. Waddell's preparations also exhibit occasional ganglion cells joined together in pairs by broad protoplasmic bridges. These may probably be regarded as belonging to the same category as binuclear ganglion cells. We do not, however, regard the ganglion cells joined together by a clearly differentiated nerve fiber as belonging to this category.

In a recent histological study of the ganglia of the sympathetic trunks in man, Stöhr, Jr. (1927), was unable to observe dendritic terminations either free or in relation to other cells. Despite the evidence to the contrary, he advanced the theory that the entire sympathetic nervous system is a great syncytial structure in which there are no free terminations except those which occur in the tissues innervated. Since he could not observe continuous protoplasmic connections between adjacent ganglion cells, he assumed that the syncytial connections are effected between ganglion cells which do not lie in immediate proximity to each other. This assumption does not seem to be warranted by the data presented.

CHAPTER III.

CENTRAL AUTONOMIC CENTERS AND CONDUCTION PATHWAYS.

Introduction.—Our present incomplete knowledge of the central autonomic centers and conduction pathways is based on both histological and physiological data. These data represent the results mainly of isolated studies of limited portions of the peripheral and central nervous systems and incidental physiological observations. Experimental study has advanced more rapidly in this field than basic histological investigation; consequently, the correct interpretation of many of the experimental findings is difficult or impossible by reason of inadequate knowledge of the histological structure and anatomical relationships of the cell aggregates in question. That the autonomic neurons in the central nervous system differ morphologically from other functional types of neurons is well known, but the range of variation in the cytological structure of these cells has not been determined with sufficient accuracy to afford an unmistakable criterion of their autonomic character. Histological and experimental methods must go hand in hand in the further investigation of the central autonomic centers.

The study of the central autonomic centers and conduction pathways from the physiological side is rendered difficult by reason of the fact that many of the visceral functions are influenced, not only by nervous impulses, but also by chemical substances or hormones circulating in the blood. For example, puncture of a certain center in the medulla oblongata results in glycosuria. This result cannot be attributed solely to the effect of stimulation of fibers which innervate the liver. Puncture of this center also stimulates fibers which innervate the adrenals, resulting in an increased output of adrenalin. This, in turn, is a factor in bringing about glycosuria. Likewise, impulses emanating from centers in the central nervous system bring about circulatory changes which, in turn, result in changes in visceral organs which are not directly connected by conduction pathways with the centers from which the nervous impulses emanated. Consequently, reactions called forth in visceral organs by stimulation of central autonomic centers may safely be regarded as the direct result of impulses emanating from the center in question only when all the possibilities of indirect influences are ruled out. In many instances indirect influences cannot

be avoided. Consequently, the results of experimental studies in this field may be regarded as least equivocal when they pertain to organs whose functions are relatively independent of changes in the blood supply and substances circulating in the blood.

MORPHOLOGY AND DISTRIBUTION OF VISCERAL NEURONS IN THE SPINAL CORD.

According to the current teaching, the preganglionic fibers of the thoracolumbar autonomic outflow arise mainly from cells in the intermediolateral cell column and in part from cells in the intermediate zone between the anterior and posterior horns. The intermediolateral cell column extends from the eighth cervical to the second lumbar segment of the spinal cord. The preganglionic fibers of the sacral autonomic outflow arise in groups of similar cells located in the intermediate zone between the anterior and posterior horns from the second sacral segment downward. The central connections of the visceral afferent components of the spinal nerves are not fully known. It may be stated, however, on the basis of both anatomical and physiological studies, that visceral afferent fibers terminate in the posterior cell column and in the apex of the posterior horn. Furthermore, the occurrence of direct visceral reflexes suggests that visceral afferent fibers also terminate in relation to the visceral efferent neurons, probably without the intervention of intercalated neurons.

In preparations of the spinal cord of animals (dogs) which were killed fourteen to eighteen days following section of the splanchnic nerves above the diaphragm, Biedl (1895) observed chromatolysis of the neurons in the intermediolateral cell column and certain small neurons in the ventral horn. Hoeber (1896) also observed retrograde changes in some of the neurons in the intermediolateral and ventral cell columns in the sixth, seventh and eighth cervical segments of the spinal cord in the rabbit following extirpation of the superior cervical sympathetic ganglion. This observation was corroborated by Huet (1898).

Onuf and Collins (1900) described chromatolysis and other degenerative changes in neurons in the dorsal cell column, and less definite changes in the small nerve cells around the central canal and in the intermediolateral cell column in cats and rabbits following extirpation of various parts of the sympathetic trunk. In certain of their animals (cats) which were killed three to six months following extirpation of the stellate ganglion, they observed diminution in the number of nerve cells in the dorsal cell column, degenerative changes in the neurons in the intermediolateral cell column and pathological changes in the paracentral nerve cells, but no unmis-

takable changes in the neurons in the intermediate zone. On the basis of these findings, they concluded that the dorsal and intermediolateral cell columns and probably the intermediate and paracentral zones contain nerve cells whose functions are essentially visceral. They regarded the cells in question in the dorsal column as afferent and all the others as efferent.

Laignel-Lavastine (1908) reported chromidial changes and atrophy in the nerve cells and diminution in their number in the dorsal and intermediolateral cell columns and paracentral and intermediate zones in the spinal cord of the dog following extirpation of portions of the sympathetic trunk. More recently Kai (1925) reported marked changes, involving diminution in the number of nerve cells, chromidial changes and other evidences of nerve cell degeneration in the spinal cord of the dog following extirpation of portions of the sympathetic trunk. According to his account, these changes were well marked ten days after operation. In the upper seven cervical segments the degenerative changes were localized in the dorsolateral region of the ventral horn and the superficial portion of the intermediate zone. Only a few nerve cells were affected in this portion of the cord. From the eighth cervical to the third lumbar segments, the most marked changes were localized in the intermediolateral cell column, less marked changes were also apparent in the dorsolateral portion of the ventral horn and the superficial portion of the intermediate zone. Kai regarded the changes described as due to retrograde degeneration; consequently, he assumed that the nerve cells affected were visceral efferent neurons.

Gagel (1928) expressed skepticism regarding Kai's findings by calling attention to the difficulties in recognizing early retrograde changes in nerve cells and in the evaluation of apparent differences in the numbers of nerve cells at symmetrical points in cross-sections of the spinal cord. Sections of the normal spinal cord not uncommonly exhibits a high degree of asymmetry in the distribution of nerve cells. In his own studies of the distribution of visceral neurons in the spinal cord in man Gagel based his conclusions mainly on the morphological characters of the nerve cells.

That the nerve cells in the intermediolateral cell column differ morphologically from both the somatic efferent neurons in the anterior horn and the afferent neurons in the posterior cell column has long been known. Jacobsohn (1908) described the nerve cells in the intermediolateral cell column in man as club- or bullet-shaped cells of medium size which exhibit an irregular distribution of chromidial substance. In general, they are closely aggregated. On the basis of histological studies, Bruce (1906) concluded that the visceral efferent neurons are not definitely limited to the inter-

mediolateral cell column. He recognized an apical group and a group situated in part in the central gray substance, which he regarded as components of the visceral column. He also emphasized the asymmetry and partial segmentation of the intermediolateral columns.

In Golgi preparations of embryos of the Chiroptera, Poljak (1924) claims to have traced axons from both the intermediolateral cell column and the intermediate zone between the dorsal and ventral horns into the ventral nerve roots. On the basis of these findings, he concluded that in this group of mammals visceral neurons occur not only in the intermediolateral cells column, but also in the entire intermediate zone.

In a recent study of the histology and topography of the visceral neurons in the spinal cord in man, Gagel (1928) described the nerve cells in the intermediolateral cell column as club- or pear-shaped or oval and approximately one-half the size of the anterior horn cells. Although, as observed in sections of the cord, many of these cells appear uni- or bipolar, he regards them all as multipolar neurons. In general, they exhibit an irregular distribution of chromidial substance. As compared with the anterior horn cells, the nucleus-plasma ratio favors the nucleus. Gagel does not regard the form of these cells as significant by reason of the fact that it is highly variable and seems to be determined, in a large measure, by the arrangement of the fibers in relation to which the cells lie, and other factors in the immediate environment. He regards the nucleus-plasma ratio and the size and distribution of the chromidial bodies as more significant than cell form.

The nerve cells in the intermediate zone, according to Gagel, commonly appear elongated or somewhat triangular, in sections of the cord, and exhibit a relatively uniform distribution of finely granular chromidial substance. Occasionally, a few larger chromidial bodies appear at the periphery of the cell body. These cells are of medium size and commonly occur in groups of two or three. As compared with the anterior horn cells, the nucleus-plasma ratio favors the nucleus. Although these cells differ morphologically from those in the intermediolateral cell column, Gagel regards them as visceral in function.

According to Gagel's findings, the intermediolateral cell column extends from the middle of the eighth cervical to the lower level of the first lumbar segment. Only a few cells which probably belong to this column were found in the second lumbar segment. These were located at the lateral border of the intermediate zone. Cells of the types described as intermediate zone cells were found in the region between the anterior and posterior horns throughout the entire length of the spinal cord.

SPINAL AUTONOMIC CENTERS.

On the basis of available anatomical and physiological data, it may be stated that vasomotor, piloerector, and sweat centers occur throughout the thoracic and upper lumbar segments of the spinal cord. For example, perspiration of the head, neck and arms is regulated through a center in the second and third thoracic segments. This center also contains the preganglionic neurons involved in the sympathetic innervation of the lacrimal glands. Perspiration of the upper trunk region is regulated through centers in the fourth to the ninth thoracic segments, that of the trunk below the umbilicus through centers in the ninth or tenth thoracic to the third lumbar segment, and that of the lower extremities through centers in the twelfth thoracic to the third lumbar segment of the spinal cord.

The pupilodilator or so-called ciliospinal center is located in the eighth cervical and first and second thoracic segments of the cord. According to the current teaching, the cardiac accelerator center is located in the same segments. Cannon, Lewis, and Britton (1926) have shown, however, that complete elimination of the cardiac accelerators in the cat requires interruption of the visceral rami or extirpation of the thoracic sympathetic trunk as low as the sixth or seventh thoracic segments. Ionescu and Enachescu (1928) also traced cardiac rami from the sympathetic trunk as low as the sixth thoracic segment in man. Consequently, it may be assumed that the corresponding segments of the spinal cord also contain cardiac accelerator neurons. The abdominal viscera receive impulses via the splanchnic nerves from centers in the fourth thoracic to the second lumbar segment of the spinal cord.

The genito-urinary and recto-anal centers are located in the upper lumbar and sacral segments of the cord. Inhibition of the detrusor muscle and contraction of the sphincter vesicæ are mediated through centers in the first and second lumbar segments. Contraction of the detrusor muscle and inhibition of the sphincter vesicæ are mediated through centers in the sacral segments of the cord. Vaso-dilatation of the erectile tissue and ejaculation are mediated through centers in the same segments. The nervous mechanism for the rectum and anus is similar to that of the detrusor muscle and sphincter vesicæ. The tonus of the sphincter ani is maintained through impulses emanating from centers in the first and second lumbar segments. Inhibition of the sphincter ani and peristaltic contraction of the colon are mediated through centers in the sacral segments of the cord.

In general, the autonomic centers in the spinal cord are not subject to direct cortical influences, but the sacral centers involved in micturition and defecation are in some degree subject to voluntary control. In infancy evacuation of the bladder and bowel

occurs automatically, but as the pyramidal tracts become functional, and the child is subjected to training, reflex micturition and defecation are brought under voluntary control, so that they may be inhibited within limits and voluntarily initiated. This voluntary control depends, in a large measure, on the voluntary innervation of the striated musculature of the external sphincters.

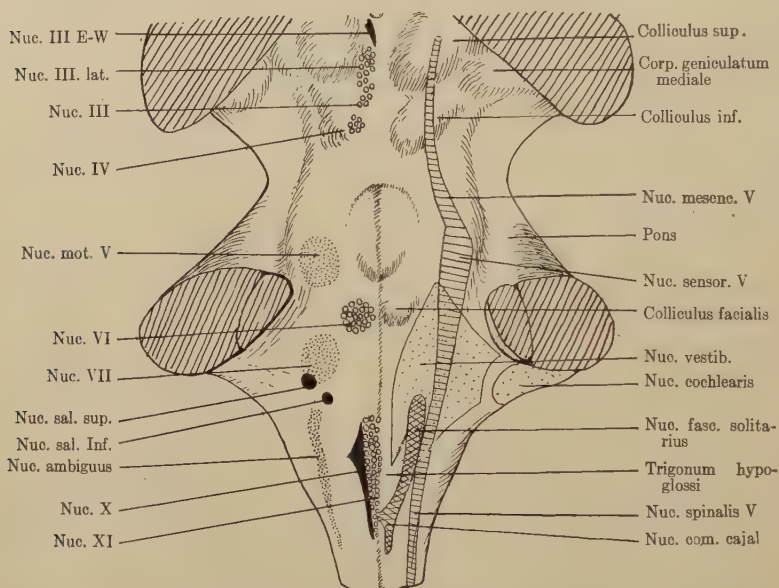


FIG. 13.--Dorsal view of the human midbrain and medulla oblongata with the positions of the cranial nerve nuclei projected on the surface. The sensory nuclei are indicated on the right side and the motor nuclei on the left. Horizontal lines indicate the general somatic sensory area; double cross-hatching, the visceral area; open stipple, the special somatic sensory area; circles, the somatic motor nuclei; solid black, the general visceral efferent nuclei; coarse stipple, the special visceral efferent nuclei.

GENERAL VISCERAL EFFERENT NUCLEI IN THE MEDULLA OBLONGATA AND MESENCEPHALON.

The general visceral efferent fibers of the cranial nerves arise from cells in a series of nuclei, viz.: the dorsal motor nucleus of the vagus, the salivatory nucleus and the Edinger-Westphal nucleus, which constitute the general visceral efferent column in the brain stem (Fig. 13). These cells are of small and medium size, with a relatively large nucleus. The chromidial substance is only poorly developed and exhibits an irregular distribution (Malone, 1913).

The dorsal motor nucleus of the vagus lies subjacent to the ala cinerea of the rhomboid fossa, along the side of the central canal, and dorsolateral to the hypoglossal nucleus. The efferent fibers

arising in this nucleus are widely distributed to the parasympathetic ganglia in relation to the thoracic and abdominal viscera for the innervation of the involuntary musculature of the heart, respiratory passages, esophagus, stomach, small intestine, liver, pancreas, kidneys, and other glands. According to Malone (1913), the dorsal motor nucleus of the vagus in the lemur and monkey contains two distinct types of nerve cells (Fig. 14). The oral portion is composed

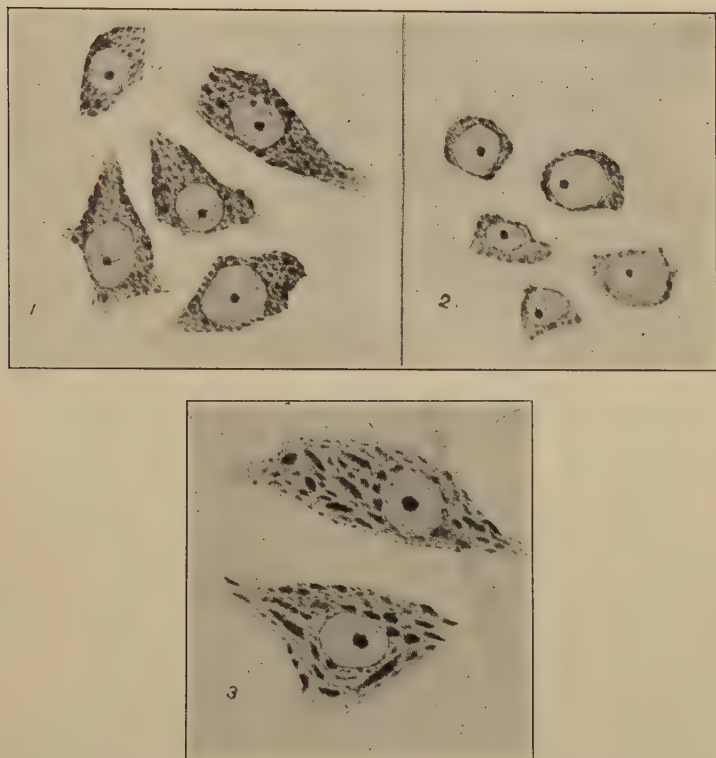


FIG. 14.—Efferent nerve cells from the medulla oblongata of the lemur: 1 and 2, visceral efferent cells from the dorsal motor nucleus of the vagus; 3, somatic efferent cells from the hypoglossal nucleus. (Malone.)

of small cells with relatively large nuclei and a meager supply of chromidial substance. The middle portion is composed of medium-sized cells with a more abundant supply of chromidial substance. The nucleus-plasma ratio of these cells, as compared with that of the small cells, favors the cytoplasm; as compared with that of the somatic motor cells, it favors the nucleus. The caudal portion is composed mainly of small cells, but contains some cells similar to the large cells in the middle portion. According to Malone, the

axons of the small cells supply smooth muscle and glands, those of the medium-sized cells supply heart muscle. On the basis of these findings, he designated the portion of the dorsal motor nucleus of the vagus which contains the medium-sized cells *nucleus cardiacus nervi vagi*.

The nucleus salivatorius lies in the reticular formation, at the junction of the pons and medulla oblongata and near the rostral end of the nucleus ambiguus. The efferent fibers arising from the more caudal portion, or *nucleus salivatorius inferior*, are conveyed via the glossopharyngeal nerve to the otic ganglion for the innervation of the parotid gland. Those arising from the rostral portion, or *nucleus salivatorius superior*, are conveyed via the chorda tympani to the submaxillary ganglion for the innervation of the submaxillary and sublingual salivary glands (Kohnstamm, 1902, 1903; Yagita, 1909).

The Edinger-Westphal nucleus is situated in the rostral portion of the nucleus of the oculomotor nerve. It is composed of small cells whose axons run in the oculomotor nerve as preganglionic fibers to the ciliary ganglion, for the innervation of the intrinsic musculature of the eye.

OTHER AUTONOMIC CENTERS IN THE MEDULLA OBLONGATA.

A vasoconstrictor center in the medulla oblongata was recognized by Owsjannikoff as early as 1871. In a series of experiments, in which the brain stem was transected at successive levels from above downward, he first observed a fall in blood pressure when the section was made at the middle level of the pons. Sections made at lower levels resulted in still further lowering the blood pressure. The results of more recent experimental studies have afforded a basis for the localization of the vasoconstrictor center in various mammals. In the rabbit it is located in the floor of the upper part of the fourth ventricle. It is a paired center, lying approximately 2.5 mm. from the median plane in a position coinciding with that of the superior olive. Section of the brain stem above this level does not affect the blood pressure. Section of the brain stem below the vasoconstrictor center results in a rapid fall in blood pressure. Obviously, the vasoconstrictor center normally maintains a state of tonus and plays an important rôle in the maintenance of normal blood pressure.

In a series of experiments involving electrical stimulation of the floor of the fourth ventricle in cats, Ranson and Billingsley (1916) observed a marked drop in blood pressure when the electrode was inserted under the clava just lateral to the obex. On the basis of this finding, they suggested that this area may contain a true

depressor center. This finding has not been fully confirmed by the results of later investigations (Schilf, 1926).

That puncture of the floor of the fourth ventricle in a definitely circumscribed area results in hyperglycemia and glycosuria was already known to Claude Bernard. Experimental data obtained by later investigators also indicate the existence of a center in the medulla oblongata which exerts a regulatory influence on sugar metabolism. In attempting to localize this so-called sugar center, Brugsch, Dressel and Lewy (1923) observed that puncture of the rostral portion of the dorsal motor nucleus of the vagus resulted in hypoglycemia, while puncture of the caudal portion of this nucleus results in hyperglycemia and glycosuria. According to Toenniesen (1924), it seems more probable that the puncture which resulted in hyperglycemia and glycosuria did not strike the vagus nucleus, but an aggregate of cells outside this nucleus which is related to the autonomic system. In view of the fact that a center exists in the diencephalon which exerts a regulatory influence on carbohydrate metabolism, it seems not impossible to explain the above results of puncture of the floor of the fourth ventricle on the assumption that descending fibers from the sugar center in the diencephalon, and not a specific group of neurons in the medulla oblongata, were stimulated. In any case, the diencephalic center must be regarded as the chief center for the nervous regulation of carbohydrate metabolism.

AUTONOMIC CENTERS IN THE DIENCEPHALON.

The diencephalic nuclei which are known to subserve autonomic functions are located in the hypothalamus and wall of the third ventricle. They are included in the older portion of the diencephalon, viz.: the paleothalamus, which, in the lower vertebrates, constitutes the highest regulatory center for visceral functions. The histological structure of this region of the forebrain has been investigated especially by Malone (1910, 1914), to whom we owe much of our present knowledge regarding the anatomical relationships of the diencephalic nuclei and the morphological characters of their constituent neurons.

The autonomic functions of the diencephalon involve mainly the tuber cinereum, corpus subthalamicum, nucleus mammillo-infundibularis and nucleus parameedianus. The tuber cinereum includes: (a) the substantia grisea centralis, (b) the nucleus supraopticus, and (c) the nucleus paraventricularis (Malone). The constituent neurons of these nuclei resemble very closely the visceral efferent neurons in the spinal cord and medulla oblongata; consequently, they may be classified as autonomic on the basis of their morphological characters. The nucleus mammillo-infundibularis (Malone) is regarded

as autonomic in function mainly on the basis of experimental data. The nucleus paramedianus (Malone), like the nuclei in the tuber cinereum, is composed of cells which resemble known autonomic neurons, and may, therefore, be regarded as autonomic. The corpus subthalamicum is regarded as autonomic mainly on the basis of experimental data.

The substantia grisea centralis occupies the wall of the third ventricle. It is best developed in the oral portion of the tuber cinereum. Farther caudally it is encroached upon by the adjacent nuclei, but occupies the interspaces between the latter. The nerve cells are small and are scattered irregularly in a delicate meshwork of fibers. In their morphological characters they resemble very closely the neurons in the intermediolateral cell column in the spinal cord (Greving, 1923).

The nucleus supraopticus lies just dorsal to the tractus opticus and in intimate relation to it. At the level of the optic chiasma, it is sharply delimited from the substantia grisea centralis. There is no sharp line of demarcation between the two formations farther caudally. The nerve cells in the nucleus supraopticus resemble those in the substantia grisea centralis in other respects, but are distinctly larger than the latter.

The nucleus paraventricularis (Malone) lies nearer the third ventricle than the nucleus supraopticus, and more dorsally. Its rostral border lies a little lower than that of the latter nucleus. It extends caudally almost to the level of the massa intermedia. The nerve cells in this nucleus are essentially similar to those in the nucleus supraopticus (Fig. 15).

The nucleus mammillo-infundibularis (Malone) is located dorso-lateral to the nuclei tuberis. It is closely related to the lateral nucleus of the corpus mammillare, but is probably distinct from the latter (Greving, 1923). It is made up of relatively large multipolar neurons.

The nucleus paramedianus (Malone) is situated in the wall of the third ventricle just dorsal to the massa intermedia and medial to the nucleus reuniens. It consists of a vertical cell column whose constituent neurons resemble very closely the neurons in the substantia grisea centralis.

The corpus subthalamicum lies in the lateral portion of the hypothalamus at the level of the hypothalamic decussation. It is composed of multipolar neurons of medium size.

Our knowledge of the localization of diencephalic centers which influence specific visceral functions rests mainly on the results of animal experimentation and is as yet incomplete. On the basis of experiments involving stimulation of the hypothalamus, Karplus and Kreidl (1909) were able to localize the diencephalic center for the control of the smooth musculature of the eye in the medial por-

tion of the corpus subthalamicum. On the basis of the results of later experiments reported by Karplus and Kreidl (1918), they concluded that the corpus subthalamicum also contains the diencephalic centers for the regulation of the lacrimal, salivary and sweat glands and the vasoconstrictor and temperature-regulating mechanisms. The results of earlier experiments reported by

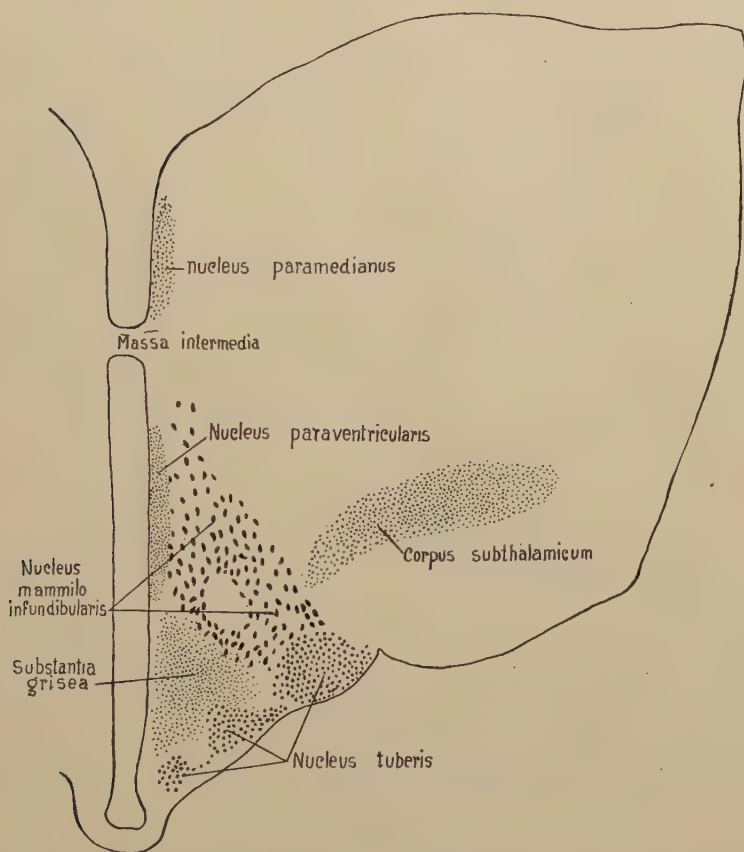


FIG. 15.—Diagrammatic cross-section of the diencephalon, showing relative positions of diencephalic autonomic nuclei.

Eisenschmidt and Schnitzler (1914) seem to indicate that the center for the regulation of body temperature is located in the tuber cinereum. Other experimental data available indicate that the chief centers for the regulation of water elimination and carbohydrate metabolism probably are localized in the tuber cinereum.

That the hypophysis plays an important rôle in various autonomic functions, particularly metabolism, is well known. The glandular

portion of this body is supplied by fibers from the plexus on the internal carotid artery (Pines, 1927). The pars intermedia and pars neuralis sustain an intimate anatomical and functional relationship to the diencephalic autonomic centers. They are connected with the nucleus supraopticus by nerve fibers which traverse the wall of the infundibulum. Greving (1928) designated these fibers the tractus supraoptico-hypophysis. That some of its fibers conduct impulses centripetally is suggested by their anatomical relationships and by experimental data. Following lesions of the posterior lobe of the hypophysis, Lewy and Kary were able to demonstrate cell changes indicative of primary stimulation, both in the nucleus supraopticus and the central part of the tuber cinereum. On the basis of these findings, Greving concluded that the nucleus supraopticus represents the center of innervation of the posterior hypophyseal lobe and regulates its hormone production. He also suggested that the nucleus paraventricularis may play a part in the functional regulation of the posterior lobe of the hypophysis by reason of its intimate relationship to the nucleus supraopticus and tuber cinereum through the tractus paraventricularis cinereus. On the basis of all the available data, including the phylogenetic development of the hypophysis, Greving regarded the diencephalic autonomic centers and the hypophysis as a functional unit.

AUTONOMIC CONDUCTION PATHWAYS IN THE MEDULLA OBLONGATA AND SPINAL CORD.

Our knowledge of the efferent fiber tracts through which impulses emanating from the autonomic centers in the diencephalon are conducted to the visceral efferent nuclei in the medulla oblongata and spinal cord is as yet meager. In the lower levels of the diencephalon, according to Isenschmidt and Schnitzler (1914), the fibers which convey impulses from the tuber cinereum lie widely scattered throughout the ventral and medial portions of the cross-section. Neither are they aggregated in compact bundles in the upper levels of the mid-brain. Nor have well-defined descending autonomic conduction pathways been described in the medulla oblongata. Yet, the existence of descending fibers in the medulla oblongata and spinal cord through which impulses from higher centers reach the visceral efferent nuclei must be conceded.

The existence of descending vasomotor conduction pathways in the spinal cord has been amply demonstrated experimentally, but the exact course of these pathways and their location in a cross-section of the cord are not known. Unilateral hemisection of the cord at the level of the upper cervical segment in cats, according to Karplus and Kreidl, regularly results in paralysis of the vessels of the extremities on the side of the lesion. In their experiments the

paralysis was diminished somewhat at the end of the first day, but was still demonstrable. They concluded, on the basis of their experimental findings, that the efferent conduction in the spinal cord of vasomotor impulses to the extremities in cats and monkeys is mainly, but not exclusively, unilateral.

That unilateral lesions of the medulla oblongata and cervical spinal cord result in pupillary constriction on the same side has long been known. Experimental hemisection of the cervical cord also results in pupillary constriction and associated ocular phenomena, but no ocular effects are produced by unilateral hemisection of the cervical cord following interruption of the cervical sympathetic trunk or extirpation of the superior cervical sympathetic ganglion on the same side.

That impulses conveyed through either lateral half of the cervical spinal cord reach the sweat glands of the extremities on both sides was demonstrated experimentally by Karplus and Kreidl in the cat. Karplus also expressed the opinion that the spinal fibers involved in the conduction of sweat secretory impulses do not constitute a compact bundle. These impulses probably are conveyed by short fibers with frequent relays in the gray matter.

It cannot be assumed, on the basis of our present knowledge, that each visceral function which is subject to regulatory influences from centers in the medulla oblongata and diencephalon is subserved by a distinct system of descending fibers in the spinal cord. Neither can it be assumed that any descending visceral conduction pathways are made up of long fibers. No long fiber tracts for the conduction of efferent visceral impulses have as yet been recognized.

The theory that certain of the visceral organs are subject to direct cortical influences has been advanced on the basis of experimental and clinical observations. In the light of our present knowledge regarding the anatomical and physiological relationships of the central autonomic centers, this theory cannot be sustained. It cannot be denied, however, that cortical processes, especially emotional excitement, influence visceral functions. In the absence of any positive data indicating the existence of cerebral centers which exert a direct influence in the regulatory control of visceral functions, or of long conduction pathways through which impulses emanating from the brain could be conveyed to individual visceral organs, it seems not improbable that a particular cerebral state may bring about a corresponding change in the general irritability of the gray matter in the medulla oblongata and spinal cord and thus exert an influence on the segmental centers through which the visceral organs in question are supplied. For example, it might be assumed, on this basis, that a state of grief, in many cases, so affects the preganglionic visceral neurons involved in the innervation of the lacrimal glands. In like manner, a state of perplexity

or fright probably affects the spinal centers through which the sweat glands are innervated. Indeed, nearly every emotional state affects the vasomotor mechanism, but each in a different manner. Worry is commonly accompanied by peripheral vasoconstriction, joy by peripheral vasodilatation, shame by an irregular distribution of vasodilatation. Such visceral reactions also have their counterparts in somatic reactions to cerebral states. For example, pleasurable emotions are reflected in the buoyant posture and movements of the body. Grief, on the other hand, is reflected in the drooping posture and slow movements of the body. Strong emotions may even result in temporary loss of muscular control under certain conditions and in the ability to exert extraordinary muscular effort under other conditions. Just as certain emotional states call forth activity of the somatic efferent neurons which innervate certain groups of voluntary muscles, without involving a special cerebral center, so it may be conceived that various cerebral states affect different groups of visceral neurons in the diencephalon, medulla oblongata and spinal cord, resulting in changes in one or more visceral functions.

CHAPTER IV.

GENERAL PHYSIOLOGY OF THE AUTONOMIC NERVOUS SYSTEM.

FUNCTIONAL CONNECTIONS OF THE AUTONOMIC WITH THE CENTRAL NERVOUS SYSTEM.

ALTHOUGH the nervous control and regulation of the vital functions of the body are carried out through the autonomic nervous system, this system is in no sense functionally independent of the central nervous system. The neurons in the autonomic ganglia and plexuses are functionally related to the central nervous system through the general visceral efferent components of the cerebrospinal nerves, viz.: the preganglionic visceral efferent neurons. The preganglionic components of the spinal nerves are analogous to the intercalated neurons in the spinal cord whose axons terminate in relation to the somatic motor neurons in the anterior horn. Consequently, the nerve cells in the ganglia of the sympathetic trunks and prevertebral plexuses may be regarded as analogous to the anterior horn cells (Chapter I). Just as the latter cannot carry out their normal functions independently of the intercalated neurons, so the autonomic neurons, in general, cannot function independently of the preganglionic visceral efferent neurons. Exceptions to this general statement, *e. g.*, the independent functional activity of the enteric plexuses, will be considered in their proper connections.

Neither can the preganglionic neurons function in the absence of the autonomic ganglia. If the autonomic ganglia are removed, the preganglionic neurons are unable to establish direct functional connections with the tissues to be innervated, even though the preganglionic and postganglionic nerves be united by operative technique. Langendorff (1901) reported two experiments on cats in which preganglionic stimulation was again effective three and a half months after extirpation of the superior cervical sympathetic ganglion. Langley and Anderson (1904) obtained an apparently similar result in 2 cases out of 8, but later microscopic examination showed that in both these cases some of the nerve cells in the superior cervical ganglion had not been removed; consequently, some of the regenerating preganglionic fibers reestablished functional connections with the remaining ganglion cells. Other experiments of the same kind, some of which involved extirpation of the ciliary, and others extirpation of the stellate ganglion, carried out by Langley, yielded only negative results.

FUNCTIONAL SIGNIFICANCE OF GANGLIONIC NEURONS.

In considering the functional significance of the autonomic neurons in the visceral efferent conduction pathways, it is important to bear in mind that a single preganglionic neuron enters into synaptic relationship with many ganglionic neurons. This may be regarded as an adaptation to bring about a relatively wide-spread effect of a single efferent impulse. Whether the efferent impulse is modified by the ganglionic neurons cannot be stated at present. The results of experiments designed to answer this question are not unequivocal. Not a few investigators have studied the effects on the pupil of section of the cervical sympathetic trunk as compared with the effects of section of the internal carotid nerve just distal to the superior cervical sympathetic ganglion. Likewise, the effects on the pupil of cervical sympathetic stimulation have been compared with those of stimulation of the postganglionic sympathetic fibers affecting the pupil. The results of such studies are not sufficiently in accord to warrant any conclusion regarding the effect of the sympathetic ganglion cells involved.

Certain investigators, acting on the assumption that the effect of the ganglionic neurons might be more readily demonstrated in the case of the nerves supplying the blood vessels than other autonomic nerves, by reason of the important rôle of the blood vessels in the nutrition of all the tissues, have carried out similar experiments involving these nerves. In some instances, the effects on certain blood vessels of stimulation of the pre- and postganglionic fibers involved were compared. In others the effects of removal of the ganglion cells was studied. In general, the results of such experiments do not indicate that the efferent impulse suffers any important modification by passing through the ganglionic neurons. The autonomic ganglia are essentially relay stations in the visceral efferent pathways. Schultz (1900) observed that effective stimulation of postganglionic fibers requires a stimulus of greater intensity than effective stimulation of the corresponding preganglionic fibers. On the basis of this observation, he advanced the opinion that impulses traversing the preganglionic fibers which are not of sufficient intensity to activate the ganglion cells may by summation reach the threshold of stimulation of the ganglionic neurons. Veach (1926) was able to show, in the case of the superior cervical sympathetic ganglion, that the pre- and postganglionic fibers are not equally sensitive to induction shocks, but he could obtain no evidence which seemed to indicate that impulses are modified quantitatively by passing through the ganglion.

In general, it may be stated that each sympathetic ganglion receives preganglionic fibers from several segments of the spinal cord. Hofmann (1904) pointed out that stimulation of a single

communicating ramus commonly results in activation of the entire end organ in question. For example, the dilator pupillæ responds as a whole to stimulation of the white communicating ramus of any one of the thoracic nerves through which it is supplied, but stimulation of postganglionic fibers contained in a single one of the long ciliary nerves results in contraction of only a limited portion of the dilator pupillæ muscle. In the reverse experiment, in which certain of the long ciliary nerves were cut previously, he also observed that stimulation of the cervical sympathetic resulted in contraction of only those parts of the dilator pupillæ which are innervated by the long ciliary nerves which remained intact. On the basis of these results, Hofmann concluded that dilatation of the entire pupil upon stimulation of a single white communicating ramus could only be explained on the assumption that functional connections exist between neurons in the superior cervical sympathetic ganglion through which impulses conveyed by a single white ramus may be communicated to all the ganglion cells involved in the innervation of the dilator pupillæ muscle. This conclusion is at variance with the results of the majority of the more recent anatomical and physiological studies. Conclusive evidence of the existence of synaptic connections between neurons in the ganglia of the sympathetic trunk is not forthcoming. Neither do we regard the assumption of such connections necessary to explain Hofmann's results. The fact that each preganglionic neuron enters into synaptic relationship with a number of ganglion cells does not preclude the possibility that the preganglionic fibers in a single white ramus may play a rôle in the innervation of the entire dilator pupillæ muscle. Furthermore, Langley (1904) pointed out that dilatation of the entire pupil is sometimes brought about by stimulation of a single long ciliary ramus. He, therefore, assumed the existence of a preterminal plexus of postganglionic fibers through which impulses conveyed by relatively few fibers might affect the entire dilator pupillæ muscle. Similar preterminal plexuses have been described in certain glands and, in isolated cases, also in the walls of blood vessels.

AFFERENT NEURONS FUNCTIONALLY ASSOCIATED WITH THE AUTONOMIC NERVOUS SYSTEM.

The nervous reactions carried out through the autonomic nerves are essentially reflex, but the afferent neurons involved in the reflex arcs are not regarded as components of the autonomic nervous system. They include both visceral and somatic afferent components of the cerebrospinal nerves. Afferent impulses arising in any part of the body may elicit reflex reactions carried out through the autonomic nervous system. The question regarding the exist-

ence of autonomic neurons which are essentially afferent in character has been much discussed. There are no data available at present which may be regarded as proving the existence of autonomic neurons which are incorporated in conducting pathways through which afferent impulses are conveyed into the central nervous system. Neither is there any clear evidence that either the ganglia of the sympathetic trunks and prevertebral plexuses or the cranial autonomic ganglia either include afferent neurons or constitute reflex centers in the ordinary sense. On the contrary, both anatomical and physiological data are available which demonstrate quite clearly that certain of the peripheral plexuses, *e. g.*, the myenteric and submucous plexuses, contain reflex mechanisms and are capable of carrying out coordinated reflex activities independently of the central nervous system (see Chapter IX).

AXON REFLEXES.

Although the data available at present speak against the existence of reflex connections in the autonomic ganglia (except in the peripheral plexuses), physiological data are not wanting which strongly suggest that reflex reactions may, under certain conditions, be carried out through these ganglia. Such data were recorded by Claude Bernard as early as 1864. Sokownin (1874) observed that after all the nervous connections of the inferior mesenteric ganglia except the hypogastric nerves were cut, stimulation of the central end of one hypogastric nerve elicited contraction of the bladder, the efferent impulses passing down the hypogastric nerve on the opposite side. Langley and Anderson (1894) confirmed this finding. They observed further that stimulation of the central end of one hypogastric nerve, under the same experimental conditions, also elicits contraction of the internal sphincter ani, pallor of the mucous membrane of the rectum, slight pallor of the opposite cornu of the uterus, and rarely slight contraction of this part of the uterus and the vagina. All these reactions were temporarily abolished by intravenous injection of nicotin. Since nicotin in the dosage employed does not abolish the effects of stimulating the peripheral ends of the hypogastric nerves, they assumed that the impulses set up in the central end of the hypogastric nerve were blocked in the inferior mesenteric ganglion. Accordingly, they concluded that the impulses which passed up the hypogastric nerve stimulated traversed nerve cells in the inferior mesenteric ganglion and were conveyed peripherally in the hypogastric nerve on the opposite side. They pointed out further that when the connections of the inferior mesenteric ganglion with the spinal nerves are cut and time is allowed for degeneration, stimulation of the central

end of the hypogastric nerve no longer elicits the reflexes described above, although stimulation of the peripheral end of the hypogastric nerve is still effective. Consequently, the reflexes in question cannot be due to neurons in the ganglion which send one fiber peripherally in one, and another in the other hypogastric nerve. Furthermore, the fibers in the central end of the hypogastric nerve which convey the impulses to the inferior mesenteric ganglion must arise from nerve cells either in the spinal cord or spinal ganglia. Consequently, the impulses must be transmitted to the neurons in the inferior mesenteric ganglion through collateral branches of these fibers.

In other experiments carried out on animals in which the spinal cord was completely destroyed or the preganglionic fibers connecting the portion of the sympathetic trunk in question with the spinal cord were severed so that no reflexes could be carried out through spinal centers, Langley (1900) found that when the sympathetic trunk was divided and its central end stimulated contraction of the erector pili muscles and constriction of the cutaneous blood vessels took place in an area corresponding to the distribution of from one to four gray rami above the level at which the stimulus was applied. These responses were also abolished by intravenous injection of nicotin or its application to the sympathetic ganglia in question. Neither could they be elicited after the preganglionic fibers in the sympathetic trunk had undergone degeneration. It seemed clear, therefore, that the reactions in question were mediated through preganglionic fibers and neurons in the ganglia of the sympathetic trunk. Langley concluded, on the basis of these findings, that each preganglionic fiber which enters the sympathetic trunk gives rise to a number of branches through which it effects synaptic connections with several, perhaps many, ganglionic neurons. The preganglionic fibers which supply a compound ganglion, *e. g.*, the superior and inferior cervical, may send all their branches to one ganglion. Those which enter a single segmental ganglion commonly traverse more than one ganglion and may give rise to branches which terminate in all these ganglia. In the lower thoracic, lumbar, and sacral portions of the sympathetic trunk in the cat, according to Langley, the majority of the preganglionic fibers send branches to three, and some to four ganglia. When such preganglionic fibers are stimulated distally, under experimental conditions, the impulse travels centralward in the fiber and peripheralward in its collateral branches and may activate all the ganglionic neurons in relation to which these branches terminate. Langley explained all reflex phenomena elicited by stimulation of the central ends of preganglionic fibers following destruction of their connections with the central nervous system on this basis. Since they could not be regarded as reflexes in the ordinary sense, he called them pseudo-reflexes.

Inasmuch as they depend on afferent conduction through preganglionic fibers, he also called them preganglionic axon reflexes.

Postganglionic axon reflexes, *i. e.*, reflexes which are carried out through a single axon and its branches, have also been described. It has been assumed that stimulation of the peripheral portion of an axon or an axon collateral may give rise to impulses which travel centralward through the division of the fiber stimulated and peripheralward through its other divisions, thus calling forth a localized response in the end organ in question. Such reactions were described by Kuhne (1886) in skeletal muscles and more recently by various investigators in both somatic and visceral organs.

Speranskaja-Stepanowa (1925) reported certain phenomena which he regarded as postganglionic sympathetic vasodilator and vasoconstrictor axon reflexes in the frog. Wernoe (1925) also described viscerocutaneous reflexes in fishes, which he regarded as reflexes mediated through a single sympathetic neuron, the axon of which sends one branch to a visceral organ and another to the skin. Certain cutaneous manifestations in man have also been interpreted as due, at least in part, to localized axon reflexes (Breslauer, 1919).

Preganglionic axon reflexes have been observed mainly under experimental conditions. Reactions which have been interpreted as postganglionic axon reflexes have been observed under both experimental and apparently normal physiological conditions. To what extent either preganglionic or postganglionic axon reflexes play a rôle in the normal functional activity of the autonomic nervous system is not known.

ANTAGONISTIC ACTION OF SYMPATHETIC AND PARASYMPATHETIC NERVES.

According to Langley's classification, as outlined in Chapter I, the autonomic nervous system is made up of the sympathetic and parasympathetic divisions. The preganglionic fibers associated with the former division are components of the thoracic and upper lumbar nerves; those associated with the latter division are components of certain of the cranial and sacral nerves. The internal organs are supplied by both sympathetic and parasympathetic nerves; consequently, they receive efferent impulses from widely separated centers in the central nervous system, the effects of which are in general antagonistic. For example, impulses reaching the heart through the vagus nerves tend to inhibit, and impulses mediated through the sympathetic cardiac nerves tend to accelerate cardiac rhythm. On the contrary, vagus impulses exert an excitatory influence on the gastro-intestinal musculature, and impulses mediated through the sympathetic nerves inhibit gastro-intestinal motility. The influence of the pelvic nerves on the large intestine

is the same as that of the vagi on the less distal parts of the alimentary canal. With regard to the genital organs, impulses conveyed through the hypogastric nerves exert a vasoconstrictor, and impulses conveyed through the pelvic nerves a vasodilator effect. The musculature of the bladder contracts in response to impulses received through the pelvic nerves, and relaxes in response to impulses received through the hypogastric nerves. Similar conditions also obtain in the cephalic region. Constriction of the pupil is brought about by impulses emanating from the mid-brain through the pre-ganglionic components of the oculomotor nerve and neurons in the ciliary ganglion. Dilatation of the pupil is mediated through pre-ganglionic fibers arising in the upper thoracic segments of the spinal cord and neurons in the superior cervical sympathetic ganglion. Likewise, the salivary glands are supplied by parasympathetic fibers from the otic and submaxillary ganglia and sympathetic fibers from the superior cervical sympathetic ganglion.

Whether the blood vessels throughout the body are innervated by both sympathetic and parasympathetic fibers must be regarded as an open question. All blood vessels probably are supplied by sympathetic fibers. The blood vessels in certain parts of the body are also known to be supplied by parasympathetic fibers. In general, the sympathetic fibers supplying blood vessels subserve vasoconstriction; the parasympathetic fibers, vasodilatation. There are no known pathways by which fibers belonging either to the cranial or sacral autonomic outflow reach the vessels of the extremities or the somatic portions of the trunk. It has been assumed by certain investigators that groups of parasympathetic cells are present in the spinal cord throughout the cervical and thoracic regions, and that these cells send their axons out through the dorsal roots of the spinal nerves to be distributed to the peripheral blood vessels. This assumption is supported by certain physiological data, but anatomical proof of the existence in the dorsal roots of the spinal nerves of efferent fibers distributed to the peripheral blood vessels is not available. Neither is it necessary to assume that all blood vessels are supplied by vasodilator fibers of parasympathetic origin. The current teaching that such is the case is based mainly on the unproved assumption that all organs which are innervated through the autonomic nervous system receive both sympathetic and parasympathetic fibers.

The sweat glands afford another instance of organs which are innervated by sympathetic, but are not known to receive parasympathetic fibers. In general, the effect of sympathetic stimulation on the sweat glands is excitatory. Although all the observed physiological activities of the sweat glands can be explained without assuming the existence of inhibitory fibers, it has been maintained by certain investigators that these glands are supplied by

inhibitory fibers of parasympathetic origin. Certain other investigators have been unable to obtain any evidence of the existence of parasympathetic fibers to the sweat glands (see Chapter XI). The assumption that all organs which are innervated through the sympathetic system also receive parasympathetic fibers, therefore, cannot be regarded as proven without exception.

The antagonistic action of the sympathetic and parasympathetic nerves may be compared with the reciprocal action of the cerebrospinal nerves which supply the flexor and extensor muscles respectively which act on a given joint. When either the flexors or extensors contract in response to nervous impulses the opposing group undergoes a degree of relaxation, but is not wholly devoid of tonus, by reason of impulses received through its efferent innervation. In like manner, the sympathetic and parasympathetic nerves supplying a given organ maintain a functional balance. For example, an increase in tonus in the cervical sympathetic, resulting in dilatation of the pupil, is accompanied by a simultaneous diminution of tonus in the parasympathetic center involved in the innervation of the sphincter pupillæ muscle. Dilatation of the pupil in response to cervical sympathetic stimulation probably is brought about, not only by contraction of the dilator pupillæ muscle, but in part also by relaxation of the sphincter pupillæ, due to diminished parasympathetic tonus. Likewise, splanchnic stimulation brings about relaxation of the gastric musculature, a result which could not be obtained without simultaneous diminution of the tonic influence of the vagus. In general, it may be assumed that increased sympathetic tonus is accompanied by a corresponding diminution of parasympathetic tonus and *vice versa*.

The principle of crossed innervation also obtains in certain of the visceral organs, *i. e.*, the stimulus which calls forth contraction of one set of muscles also calls forth simultaneous inhibition of an opposing set. For example, stimulation of the pelvic nerve elicits contraction of the detrusor muscle and relaxation of the sphincter vesicæ. On the contrary, stimulation of the hypogastric nerve elicits contraction of the sphincter vesicæ and relaxation of the detrusor muscle. These reactions also illustrate the general principle that stimulation of an inhibitory nerve may actually bring about diminution of the tonus of the musculature involved.

Although the sympathetic and parasympathetic nerves supplying a given organ usually produce opposite effects, a single nerve may contain both excitatory and inhibitory fibers. In general, the vagus fibers supplying the bronchial and gastro-intestinal musculature exert an excitatory, and those supplying the heart an inhibitory influence. On the contrary, the sympathetic fibers supplying the bronchial and gastro-intestinal musculature exert an inhibitory, and those supplying the heart and blood vessels an excitatory

influence. Either the vagus or sympathetic supply to a given organ may contain both excitatory and inhibitory fibers, but the great majority of the fibers in either the vagus or sympathetic rami involved are of the same functional type.

REGULATION OF AUTONOMIC FUNCTIONS THROUGH DIENTEPHALIC CENTERS.

Although the nervous reactions mediated through the autonomic system are essentially reflex; they also involve centers and conduction pathways in the central nervous system. For example, strong afferent impulses reaching the central nervous system through any peripheral nerve may call forth autonomic reflex responses in various parts of the body. The chief central autonomic center is located in the diencephalon. This center comprises a number of nuclei in the hypothalamus and wall of the third ventricle, including the portion of the diencephalon which is phylogenetically the oldest (see Chapter III).

On the basis of available physiological data, the autonomic center in the diencephalon may be regarded as superimposed on the lower autonomic mechanisms, over which it exercises a regulatory influence and thus plays an important rôle in the general functioning of the visceral organs. Such regulatory control of the autonomic functions probably is of much greater importance in those animals whose existence depends on their capacity to maintain a constant body temperature, viz.: birds and mammals, than in the lower vertebrates. The visceral functions which are known to be influenced by impulses emanating from the diencephalon include: (a) control of the smooth musculature of the eye, (b) contraction of the urinary bladder and uterus, (c) temperature regulation, (d) vasomotility, (e) secretory activity of the salivary, lacrimal, sweat, sebaceous and other glands, (f) water elimination, (g) carbohydrate and protein metabolism, and (h) trophic regulation of the skin and subcutaneous fatty tissue.

That impulses emanating from the diencephalon affect the smooth musculature of the eye was first demonstrated by Karplus and Kreidl (1909). In experiments carried out on cats and dogs, they observed maximum dilatation of the pupil, separation of the eyelids and retraction of the nictitating membrane in response to stimulation of the hypothalamus in the region of the corpus subthalamicum. That the reactions of the eye musculature to stimulation of this center do not depend on cortical connections was demonstrated by the results of further experiments of Karplus and Kreidl, in which they observed reflex dilatation of the pupil in response to afferent stimulation of the sciatic nerve, following

removal of the forebrain above the corpus subthalamicum. On the basis of these results, they concluded that afferent impulses which give rise to pain, on reaching the thalamus, are conveyed in part to the cortex and in part to autonomic centers in the diencephalon through which they elicit visceral reflex reactions. Many of the visceral reflex phenomena accompanying painful sensations, *e. g.*, pupillary reactions, vasomotor disturbances, perspiration, cardiac acceleration, contraction of the bladder, etc., probably are brought about in this manner. The efferent impulses involved descend in the brain stem and spinal cord and are conveyed to the visceral organs through the sympathetic and parasympathetic nerves.

In view of the facts that the administration of drugs which stimulate the sympathetic nerves (adrenalin, cocain, caffen, etc.) is followed by elevation, and the administration of drugs which stimulate the parasympathetic nerves (pilocarpin, veratrin, picrotoxin, etc.) is followed by depression of body temperature, Meyer (1913) advanced the theory that the diencephalic center for the regulation of body temperature includes an aggregate of cells, the stimulation of which influences the sympathetic nerves, bringing about a rise in temperature, and another aggregate, the stimulation of which influences the parasympathetic nerves, bringing about a fall in temperature. In general, it has been shown that the sympathetic system mediates metabolic processes through which heat is liberated, while the parasympathetic system mediates metabolic processes through which heat is conserved.

Aronsohn and Sachs (1885) produced fever in experimental animals by a stab wound in the corpus striatum. Inasmuch as the fever might have been a non-specific result of the lesion, they inserted a metallic instrument into the corpus striatum and left it there until the body temperature returned to normal, which required one to two days. After this they applied electrical stimulation, using the instrument which remained in the brain as the electrode. This procedure resulted in a rise in body temperature comparable to that observed following the initial stab wound. This result suggested the existence of a temperature-regulating center in the corpus striatum. Barbour (1912) produced a rise in body temperature by lowering the temperature of an instrument inserted into the corpus striatum, and a fall in body temperature by increasing the temperature of the inserted instrument. In view of these results, the existence of a temperature center in the corpus striatum must be conceded, but the temperature-regulating center in the diencephalon is of greater importance than the latter and may function independently of it. According to Isenschmidt and Schnitzler (1914), normal body temperature may be maintained in experimental animals following extirpation of the cerebral hemispheres, including the corpora striata, but the capacity to maintain

normal body temperature is lost following destruction of the diencephalic temperature-regulating center.

The end organs through which the nervous regulation of body temperature is brought about are mainly the blood vessels, sweat glands, and the internal organs whose metabolic processes tend to increase or inhibit heat production. The glands of internal secretion also play an important rôle in the regulation of body temperature. Although not entirely free from nervous influences, these glands may, through their secretory activity, exert a direct influence on the metabolic processes through which heat is generated. On the other hand, the temperature-regulating center may be activated directly by endocrin products in the blood stream. In view of the many factors which influence the production and elimination of heat, it is obvious that the organs involved in heat production and heat elimination must receive excitatory and inhibitory impulses from the temperature-regulating center more or less constantly. On the other hand, this center must be influenced by every variation in temperature, both at the periphery and in the internal organs, in part through nervous conduction, but mainly through the direct effect of the circulating blood on the temperature-regulating center.

The reactions of the temperature-regulating center to the temperature of the blood flowing through it probably are of greater importance in the regulation of the body temperature than the reflex responses to thermal stimulation of the peripheral receptors. In experiments carried out by Kahn (1904), raising the temperature of the blood in the carotid artery resulted in peripheral vasodilatation, perspiration and heat dyspnea, all of which are common symptoms of overheating. On the contrary, cooling of the blood supplying the hypothalamus resulted in increased metabolism in the internal organs and a consequent rise in body temperature. Barbour (1912, 1913) and Hashimoto (1915) also found that changes in the body temperature can be brought about by changing the temperature of the heat-regulating center by introducing water through fine cannulae inserted into the brain. When cold water was introduced the body temperature was raised; when warm water was introduced the body temperature was lowered.

In view of the physiological relationships of the temperature-regulating center, we should expect that any pathological condition which affects this center directly, initiates strong afferent impulses which reach the thalamus, or gives rise to toxic substances which circulate in the blood, might give rise to pathological changes in body temperature. The majority of the stimuli which give rise to fever probably exert a direct effect on the temperature-regulating center. It has also been shown experimentally that fever may be produced by a variety of mechanical, chemical and physico-chemical

stimuli (Greving, 1923). Such experimental findings afford a basis for the explanation of the constant occurrence of fever in certain cases of brain injury or other pathological lesions in the brain substance in proximity to the temperature-regulating centers, in which infection is not a factor. Likewise, such conditions as internal hydrocephalus and hemorrhage in the third ventricle may give rise to fever by reason of mechanical pressure exerted on the tuber cinereum. High fever accompanying apoplexy is due, in many cases, not alone to absorption, but in part also to the effect of pressure on the temperature-regulating center brought about by the hemorrhage which caused the apoplexy. Pathological conditions which result in great pressure on the hypothalamus, *e. g.*, certain cases of hydrocephalus, may also cause a fall in body temperature by reason of paralysis of the temperature-regulating center.

Disorders of the endocrin glands also give rise to disturbances of the body temperature. Inasmuch as certain of these glands produce hormones which play a part in the regulation of body temperature under normal physiological conditions, their dysfunction must necessarily disturb the balance of the factors involved in temperature regulation. For example, hypofunction of the thyroid gland, as manifested in myxedema, tends to depress the body temperature. On the contrary, hyperfunction of the thyroid gland is not uncommonly accompanied by a rise in body temperature. Likewise, dysfunction of the hypophysis and adrenal glands commonly give rise to disturbances of body temperature. Extirpation of the hypophysis is followed by a fall in body temperature which persists despite the administration of pyrogenic agents (Greving, 1923). Extirpation of the adrenals is also followed by a fall in body temperature. The abnormally low body temperature observed in cases of Addison's disease must also be attributed to the destruction of adrenal tissue.

Cawadias (1920) advanced the theory that certain long-continued fevers not caused by infection or intoxication are the result of endocrin disorders. Cramer (1920) also advanced the theory that heat stroke is the result of excessive activity of the thyroid-adrenal apparatus, which brings about long-continued sympathetic stimulation, resulting in an overproduction of heat, and at the same time prevents normal heat elimination by reason of constriction of the peripheral blood vessels. Although this theory is not supported by extensive data, it is highly suggestive and challenges further investigation.

That carbohydrate metabolism and the elimination of water are regulated, at least in part, by nervous influences has long been known. In Claude Bernard's experiments in this field puncture of the floor of the fourth ventricle resulted in glycosuria and polyuria. Eckhart showed, as early as 1876, that polyuria may also be pro-

duced by stimulation of the corpus mamillare. The data available at present show clearly that the chief centers for the regulation of water elimination and carbohydrate metabolism are located in the hypothalamus. They probably are localized in the tuber cinereum (Leschke, 1913, 1920; Greving, 1923).

Protein metabolism is also subject to regulatory influences emanating from the diencephalon. Stimulation of the hypothalamus inhibits (Leschke and Schneider, 1918), and elimination of the diencephalic influence by section of the cervical spinal cord accelerates protein metabolism (Freund and Grafe, 1912, 1913). The regulatory influence exerted by the diencephalic center in question is essentially inhibitory.

On the basis of clinical and pathological data obtained mainly in cases of dystrophia adiposogenitalis, it may be assumed that the diencephalon also contains a center which exerts an important influence in the deposition, distribution and consumption of fat, especially in the subcutaneous tissue. Fröhlich (1901), who first studied dystrophia adiposogenitalis intensively, advanced the opinion, on the basis of his findings, that it has its cause in a lesion of the hypophysis. Erdheim (1904) pointed out, on the basis of histological studies of the hypophysis in cases of this disease, that it may exist in patients whose hypophysis is histologically intact. On the other hand, he also found the disease associated with hypophyseal tumors. The results of his studies and those of other investigators indicate that dysfunction of the hypophysis is not the cause of dystrophia adiposogenitalis, but that this disease may be caused by the effect of a hypophyseal tumor on an adjacent center in the diencephalon. On the basis of abundant clinical and experimental observations, particularly those of Göring (1922), the existence of a center in the floor of the third ventricle which exerts a regulatory influence on the deposition and consumption of fat seems to be established.

THE AUTONOMIC NERVOUS SYSTEM IN RELATION TO THE ENDOCRIN GLANDS.

The existence of a functional interdependence of the autonomic nervous system and endocrin glands is demonstrated by many physiological phenomena. This relationship is deep seated and may be regarded as a result of long-continued evolutionary processes. The most primitive forms of animal life respond mainly to chemical stimuli. These responses are inadequate to meet the needs of higher animals. The development of a nervous system through which rapid conduction and widespread coördination can be accomplished is a comparatively late event in evolution. In all the higher animals, reactions to environmental factors, as well as

the regulatory control of the internal organs, are dominated by the nervous system, but chemical stimulants still play an important rôle in the functional regulation of the internal organs. As differentiation advanced, the chemical stimulants became concentrated and specialized in the ductless glands, and there arose a reciprocal relationship between these glands and the innervation of the internal organs through which a delicate balance of the vital functions is maintained. Clearly, the first purpose for which rapid conduction and coördination became vital is self-preservation. By reason of the wide distribution of efferent impulses made possible by the synaptic connections of a single preganglionic fiber with many ganglionic neurons, the autonomic nervous system is especially adapted for rapid and widespread reactions. In these reactions the autonomic nerves stimulate the secretion of the endocrin glands; these secretions in turn augment the responses called forth through the autonomic nervous system.

The Adrenals.—Langley's generalization, that the effect of adrenalin on any part of the body is the same as the effect of stimulation of its sympathetic nerves, expresses one of the fundamental reciprocal relationships of nervous and chemical stimuli. Although there are certain exceptions to this generalization, it may be stated that in general sympathetic stimulation excites the secretion of adrenalin, and adrenalin increases reactivity to sympathetic stimulation.

Not a few investigators have observed an increase in the amount of adrenalin in the circulation due to sympathetic stimulation. Cannon and de la Paz (1911) also reported an increase in the adrenalin output due to emotional stimulation. This observation has since been corroborated repeatedly, particularly by Cannon and his associates. That adrenalin exerts an influence on the resistance of voluntary muscle to fatigue has long been known (Oliver and Schaefer, 1895). How this result is brought about is not definitely known. According to Gruber (1913), adrenalin does not lower the threshold of stimulation for normal muscle, but it promptly increases the irritability of fatigued muscle, even when a rise in blood pressure is prevented. Adrenalin also plays an essential rôle in calling forth stored carbohydrate, thus increasing the sugar content of the blood. It also plays a part in distributing the blood to the heart, lungs, central nervous system and limbs, and in reducing the supply to the abdominal organs while the latter are inhibited (Cannon, 1915). These facts, according to Cannon, "are associated with some of the most primitive experiences in the life of higher organisms, experiences common to all, both man and beast, the elementary experiences of pain, fear and rage, that come suddenly in critical emergencies."

Although the theory of the emergency action of adrenalin is based on the results of extensive investigations, it has been vigor-

ously opposed by certain investigators, notably Stewart and Rogoff (1916, 1917). The latter found no conclusive evidence that adrenalin is brought into play in a marked degree by emotional stresses or physical strains.

In a recent study of the influence of motion and emotion on adrenalin secretion, Cannon and Britton (1927) were able to confirm the conclusion, based on the results of earlier studies of Cannon and his associates, that muscular activity and emotional excitement increase the output of adrenalin. Taking the increased rate of the denervated heart as a rough measure of the increase of adrenalin in the blood, they found that the output of adrenalin was increased by even minor bodily movements. Extending the limbs or turning the body of a cat with denervated heart, in their experiments, was accompanied by an increase in the heart-rate of 5 to 10 beats per minute. Walking increased the rate 10 to 20 beats. When the adrenal glands were inactivated, the same activities were accompanied by but slight acceleration of the heart or none at all. Emotional excitement resulted in an even greater increase in the rate of the denervated heart. The same excitement of the same animals, following inactivation of the adrenal glands, resulted in but slight cardiac acceleration or none at all. Great emotional excitement plus vigorous activity in cats with denervated heart, caused an increase in the heart-rate of 30 to 80 beats per minute while the adrenals were intact, but usually only 8 beats or less following inactivation of the adrenal glands. In view of these results, they suggested that "the increased secretion of adrenin accompanying incidental and routine muscular movements such as walking, its greater concentration in the blood during muscular exercise and its abundant outpouring as a consequence of vigorous struggle emphasize the probable significance of adrenin for efficient use of muscles in the body."

The finding that even slight muscular exertion calls forth increased adrenalin secretion might seem to be incompatible with the emergency theory previously advocated by Cannon and his associates. It seems to indicate that what takes place on a large scale in emergencies takes place on a smaller scale in the ordinary behavior of the organism. Cannon and Britton, therefore, suggested that "the emergency theory would have to be altered insofar as it might imply that the sympathico-adrenal mechanism is called into action only at times of violent emotion. According to the evidence now in hand, the greater the emergency, as measured by intensity of excitement and struggle, the more is that mechanism utilized."

Persistence of the visceral concomitants of emotional excitement for some time after the stimulus has ceased to act is a fact of common experience. In the experiments of Cannon and Britton, this was attributed solely to continued adrenal secretion. According to

these authors, "this extension of the visceral disturbances in time has a bearing on conduct in an exciting situation, as well as thereafter. It points out the natural effect of the full expression of fear or rage, and shows the importance of limiting that expression if a persistent state of disquiet is to be avoided. It also corroborates the counsel that when bodily functions are dominated by sympathetic influences, as in the more powerful emotions, the exercise of opposed functions should not be attempted. Thus, the digestive processes, which are inhibited by excitement, may continue to be disturbed for a considerable period, and digestion cannot proceed properly until a state of calm has been restored."

Although the commonly observed effect of the injection of adrenalin on the vasomotor mechanism is a rise in blood pressure, it has long been known that the injection of adrenalin in high dilutions may, under certain conditions, result in a fall in blood pressure (Moore and Purinton, 1900). Neither does elimination of the normal output of adrenalin by ligation of the adrenal vessels necessarily result in an appreciable fall in blood pressure for a period of at least several hours, as should be expected if the sympathetic nerves were kept in tonus by adrenal secretion (Young and Lehman, 1908; Hoskins and McClure, 1912). In certain animals (cats and dogs), the administration of adrenalin in appropriate dosage may result in inhibition of gastro-intestinal peristalsis without causing a rise in blood pressure (Hoskins and McClure, 1912; Durant, 1925).

If the blood pressure were maintained by a constant minimal discharge of adrenalin, as has been assumed by many, any increase in the quantity of this substance should result in a rise in blood pressure. Yet, very dilute solutions may be injected without any effect on blood pressure. Hoskins and McClure (1912) reported that when the rate of injection of such a dilute solution is increased the threshold of stimulation is reached and the blood pressure, instead of rising, falls. On the basis of this observation, they advanced the opinion that if the adrenals exert any constant effect by continuous secretion of adrenalin it must be a depressor effect. In another series of experiments, Hoskins (1915) found that the slow infusion of adrenalin into the blood stream of an adrenalectomized dog resulted, not in increased sympathetic irritability, as indicated by the reaction to nicotine, but an actual decrease in sympathetic reactivity. This finding was corroborated by Hoskins and Rowley (1915) in a relatively large series of dogs.

On the basis of the above findings and other experimental data, Hoskins (1927) advanced the opinion that adrenalin "consistently and generally exerts a biphasic effect as it has been shown to do in cases of intestinal peristalsis, uterine contractions, and blood vessels in muscles. In that case it would serve, under ordinary conditions, if present at all, as a sympathetic sedative, as does calcium, another

normal constituent of the blood. Under other conditions its stimulating effect would come into play." Although this view may seem paradoxical, it is not incompatible with the experimental data which indicate only a stimulating effect of adrenalin. It also conforms precisely to Verworn's theory that inhibition, in general, is due to subminimal stimulation.

The Thyroid Gland.—The thyroid gland, like the adrenals, is activated by sympathetic stimulation and in turn increases the effects of sympathetic stimulation. It is brought into play whenever the defensive mechanisms of the body are called upon, regardless of whether the defensive reaction demands an exhibition of muscular energy or is directed against a bacterial infection. In the latter case the thyroid plays a rôle in the febrile reaction.

The thyroid gland sustains a close functional relationship to the reproductive organs, and special demands are made upon it particularly at puberty and during pregnancy. If these demands or the demands made on the thyroid gland by infections and intoxications exceed the physiological limits, pathological changes ensue which usually involve enlargement of the gland. In exophthalmic goiter the thyroid is over-stimulated. The colloid reserves are soon depleted and the secretory tissue undergoes compensatory hypertrophy. Sympathetic hyperexcitability is manifested in the exophthalmos, rapid pulse, perspiration and diminished gastric secretion. Not uncommonly the blood sugar is increased and there is a tendency to glycosuria and pigmentation of the skin. The whole emotional apparatus is highly stimulated and the brain thresholds are lowered to stimuli of all kinds.

That this continuous stimulation of the thyroid may lead to its exhaustion and be followed by a condition resembling myxedema is also well known. In certain cases the enlargement of the thyroid subsides, but the signs of sympathetic stimulation, viz.: tremor, tachycardia, nervousness, etc., continue. Possibly, in all these cases the adrenals are also involved; however, the manifestations of continued sympathetic stimulation, as the thyroid approaches exhaustion or becomes less irritable, can be explained without assuming any abnormal activity on the part of the adrenals.

The Pituitary Body.—The pituitary body, like the adrenals, is partly nervous in origin. Like the thyroid, its glandular portion is derived from the alimentary canal. Its functional association with the autonomic nervous system is less obvious than that of the adrenals and thyroid. That it exerts a definite influence on the growth of the osseous system and the development and function of the genital organs is well known. The posterior lobe also plays an important rôle in the regulatory control of metabolism and the deposition of fat and exerts a definite influence on the function of all involuntary muscle. It has also been maintained, on the basis of

extensive clinical and experimental data, that pituitary dysfunction plays an important rôle in certain cases of glycosuria and the type of polyuria commonly known as diabetes insipidus. On the contrary, it has been maintained, particularly by the French school headed by Camus and Roussy, that most of the disorders which have been attributed to pituitary dysfunction, *e. g.*, changes in the osseous system, diabetes insipidus, etc., are referable to lesions of adjacent areas of the hypothalamus, and not to lesions of the pituitary gland. Although the effect of pituitrin on the smooth musculature and the influence of pituitary dysfunction in certain pathological conditions are unmistakable, the data available at present afford no adequate basis for any definite conclusions regarding a direct functional relationship of the pituitary gland to the autonomic nervous system.

In summing up the relationships between the adrenal, thyroid and pituitary bodies and the autonomic nervous system, it may be stated that the secretions of all these glands tends to increase the percentage of sugar in the blood and to diminish carbohydrate tolerance. With certain exceptions, adrenalin imitates the effect of sympathetic stimulation. Thyroid secretion promotes all the catabolic activities of the sympathetic nerves. Not only is the secretory activity of the adrenals and thyroid excited through the sympathetic nerves, but their secretions in turn increase the responses of other tissues to sympathetic stimulation. A similar reciprocal relationship between the sympathetic nerves and the pituitary body has not been observed.

THE ACTION OF DRUGS ON THE SYMPATHETIC AND PARASYMPATHETIC NERVES.

Our present knowledge of the functional relationships of the sympathetic and parasympathetic nerves is based in a large measure on the results of experimental studies involving the action of various pharmacological agents on the organs innervated by the autonomic nervous system. Certain poisons, *e. g.*, nicotine, affect both the sympathetic and parasympathetic nerves in essentially the same manner. Other pharmacological agents exert a specific action on one or the other division of the autonomic nervous system, but not on both. Adrenalin and certain other substances produce effects which, with certain exceptions, are similar to the effects produced by stimulating sympathetic nerves. Pilocarpin, muscarin, physostigmin and cholin produce effects which are, in most cases, similar to the effects produced by stimulating parasympathetic nerves. Likewise, ergotoxin (Dale, 1906, 1909) and ergotamin (Dale and Spiro, 1922) paralyze the terminal structure of the sympathetic motor fibers, while atropin has the same effect on the

terminations of the parasympathetic fibers. These facts indicate a fundamental chemical difference between the sympathetic and parasympathetic nerves. They also have an important bearing on the action of hormones on the tissues. In a recent study of the effect of adrenalin, atropin and ergotamin on the denervated heart of the dog, Enderlen and Eismayer (1927) found that, although in some of their experiments the pharmacological effect of these drugs was lost for a short time, it soon returned and did not differ in any way from the effect on the normal heart. These results are in full accord with the well-known view of Langley, that sympathetico-dynamic substances influence organs with autonomic innervation even after deprivation of their nerve supply.

The essential functional relationship between the preganglionic and ganglionic neurons was discovered by the use of nicotin. Langley first observed that when a nicotin solution is applied to an autonomic ganglion, regardless of whether it belongs to the sympathetic or parasympathetic system, stimulation of the preganglionic fibers is no longer effective, although stimulation of the postganglionic fibers still elicits the characteristic response. Similar results were also obtained when a weak solution of nicotin was injected into the blood stream. He concluded, therefore, that nicotin acts on the synaptic connections of the preganglionic with the ganglionic neurons to prevent conduction through these neuron junctions. Bayliss and Starling (1899) observed the same effect of small doses of nicotin on the visceral efferent chains supplying the gastro-enteric musculature. This result led them to conclude that all effects of the vagus on the intestinal musculature are completely abolished by minimal doses of nicotin (0.3 cc. of a 1 per cent solution). This observation of Bayliss and Starling has been corroborated by not a few later investigators. When nicotin is administered in gradually increasing doses, however, stimulation of the vagus nerves again becomes effective when 25 to 50 mgm. per kilo. of body weight has been administered (Thomas and Kuntz, 1926). In our experiments still larger doses of nicotin (50 to 500 mgm. per kilo.) further augmented the responses of the intestinal muscle to vagus stimulation, so that the amplitude of the contractions in response to the same stimulus became greater than before nicotin was administered. Massive doses of nicotin (2000 mgm. or over per kilo.) finally caused paralysis of the intestinal vagi from which they did not recover during the period of observation. These findings were corroborated by the recent work of Mulinos (1927) on the cat.

Adrenalin, though produced within the body, may be regarded as representative of those drugs whose effect is similar to that of sympathetic stimulation. In general, this substance acts on all structures which are influenced by the sympathetic nerves. Accord-

ing to Langley (1921), the only structures normally innervated by sympathetic nerves which are not influenced by adrenalin after section of their nerve supply are the sweat glands of the cat and some other mammals. Comparison of the effects of sympathetic stimulation and adrenalin, however, reveals some instances in which the lack of correspondence is striking. For example, weak sympathetic stimulation in the cat causes contraction of the cutaneous arteries, the tunica dartos and the erector pili muscles, but adrenalin does not affect these structures equally. Contraction of the cutaneous arteries is brought about by a small amount, contraction of the tunica dartos by a somewhat larger amount, and contraction of the erector pili muscles by a much larger amount of adrenalin (Langley, 1921). Furthermore, certain effects have been obtained with adrenalin which have not been obtained by sympathetic stimulation. For example, Luckhart and Carlson (1921) found that adrenalin causes contraction of the pulmonary arteries of the frog and turtle, but sympathetic stimulation does not. They also found that the vasoconstrictor fibers for the lungs are components of the vagi in these animals and are paralyzed by atropin.

The most striking effect of adrenalin is manifested in its action on the blood vessels. The application of a weak solution of adrenalin to a mucous surface is commonly followed by vigorous contraction of the superficial vessels. The coronary and renal vessels do not react in this manner, but dilate following an initial constriction. This result suggests that the sympathetic nerves may also convey vasodilator fibers to these vessels. The administration of adrenalin is commonly followed by a rise in blood pressure. This cannot be due to vasoconstriction alone, since under experimental conditions vasoconstriction alone does not result in increased blood pressure. It may be assumed, therefore, that the rise in blood pressure is due in part to the direct action of adrenalin on the heart. The retardation of the heart action which follows the administration of adrenalin under certain conditions probably is due chiefly to reflex stimulation of the vagus centers. The reaction of the bronchial musculature to adrenalin simulates the effect of atropin. This probably is due to the stimulating effect of adrenalin on the endings of the broncho-inhibitor fibers. The beneficial results of adrenalin in cases of bronchial asthma probably depend on this reaction. Asthmatic patients with low blood pressure, however, may react to adrenalin in a paradoxical manner, *i. e.*, the rise in blood pressure brought about by the adrenalin may bring on an asthmatic attack (Regelsberger, 1924).

The pharmacological agents which act on the parasympathetic are more numerous than those which act on the sympathetic nerves, but their effects are less specific than the effects of adrenalin on the sympathetic system. For example, the effect of muscarin is manifested mainly in modified heart action; that of cholin in stimulation

of the intestinal musculature. Pilocarpin produces nearly all the effects which are produced by stimulation of parasympathetic nerves (Langley, 1921), but the degree of the effect produced by pilocarpin and parasympathetic stimulation is not always the same. The difference in the intensity of the effect of pilocarpin and parasympathetic stimulation is particularly marked in the small intestine. Furthermore, the action of pilocarpin is not confined to the tissues innervated by the parasympathetic nerves. For example, it causes secretory activity of the sweat glands, although they are innervated by sympathetic fibers (see Chapter XI). It also causes contraction of the spleen, an effect which is not known to be produced by vagus stimulation.

In general, atropin prevents the effects of parasympathetic stimulation, but its effects are not limited to the parasympathetic nerves. Like pilocarpin, it prevents the secretory activity of the sweat glands in the cat's paw pads, although these glands are supplied by sympathetic secretory fibers (Langley, 1878). According to Mislawski and Borman (1892), it also paralyzes the sympathetic secretory endings in the prostate gland.

Various authors have called attention to the fact that the effect of drugs which act on the sympathetic or parasympathetic nerves may, under certain conditions, be reversed. For example, Pearce (1913) found in perfusion experiments on the frog's heart that after perfusion with a pure solution of sodium chloride a small amount of adrenalin caused vasodilatation, provided curare had been given, and occasionally without it. In the experiments of BurrIDGE (1912) the administration of adrenalin after perfusion with a 3 per cent solution of sodium phosphate caused diastolic cessation of the heart beat in the frog. Kolm and Pick (1920) observed the same effect of adrenalin after decreasing the calcium content of the perfusion liquid. They also found that adrenalin caused cessation of the heart in diastole when given after a certain amount of acetylcholin. Since this effect was prevented by atropin, they attributed it to stimulation of the end apparatus of vagus fibers. In the experiments of Snyder and Campbell (1920), the action of very dilute adrenalin changed from vasoconstriction to vasodilatation when the solution was made slightly acid.

That nicotin and similar poisons exert their influence mainly on the neuron junctions is generally conceded. Nicotin in massive doses also paralyzes the nerve endings. The seat of action of drugs which, like adrenalin and pilocarpin, exert an influence mainly in relation to either the sympathetic or parasympathetic nerves has been much discussed. That it is at the junction of the postganglionic nerve fibers with the end organ is quite generally conceded, but there is no general agreement regarding the rôle of the nerve fiber termination or the component parts of the tissue elements which may be regarded as the receptors of the drug influence.

CHAPTER V.

DEVELOPMENT OF THE AUTONOMIC NERVOUS SYSTEM.

HISTORICAL SURVEY.

THE autonomic nervous system is related developmentally to the cerebrospinal nervous system. Its primordia arise relatively early in embryonic development and are composed of cells which are displaced peripherally from the neural tube and cerebrospinal ganglia. The majority of the early investigators, including Balfour (1877), Schenck and Birdsall (1878), Onodi (1886), His, Sr. (1890), His, Jr. (1891), Marshall (1893), Hoffmann (1900, 1902), and Kohn (1905, 1907), supported the theory that the cells which make up the primordia of the ganglia of the sympathetic trunks and prevertebral plexuses are derived exclusively from the spinal ganglia or neural crests. The development of the autonomic plexuses located farther peripherally, *e. g.*, the cardiac, pulmonary and enteric plexuses, was not studied intensively by these early investigators, but it was quite generally assumed that the nerve cells in all the autonomic ganglia except those in the head are derived from the same cerebrospinal sources.

Froriep (1907) traced cells of medullary origin into the primordia of the sympathetic trunks via the ventral nerve roots and communicating rami, and advanced the opinion that it is mainly these cells which become differentiated into sympathetic ganglion cells. Cajal (1908) also expressed the opinion, on the basis of his findings, that the sympathetic ganglion cells arise mainly from cells derived from the neural tube.

The early data bearing on the development of the autonomic ganglia in the head, except the ciliary ganglion, are fragmentary. Hoffmann (1885), Ewart (1890) and Chiarugi (1894) supported the theory that the primordium of the ciliary ganglion is made up of cells which are displaced from the semilunar ganglion either directly or via the ophthalmic nerve. Beraneck (1884), Reuter (1897), and Rex (1900) described the primordium of the ciliary ganglion as arising in connection with the oculomotor nerve, but they did not determine the sources of its cells. Carpenter (1906) described the early primordium of the ciliary ganglion in the chick as composed of cells which are displaced from the mid-brain via the oculomotor nerve. According to his account, this primordium also receives cells later from the semilunar ganglion via the ophthalmic nerve. In the absence of adequate data bearing on the development of the

other autonomic ganglia in the head, it was quite generally assumed that the sphenopalatine, otic and submaxillary ganglia arise from primordia composed exclusively of cells derived from the semilunar ganglion.

Such, in brief, was the status of our knowledge of the development of the autonomic nervous system when the present writer initiated a series of studies on the development of this system and its histogenetic relationship to the cerebrospinal nervous system. The results of the earlier studies in this series (1909-1914) showed clearly that the autonomic ganglia bear the same histogenetic relationship to the cerebrospinal nervous system in all classes of vertebrates, although they may differ somewhat in their morphogenesis in the several classes. The observations of Froriep and Cajal regarding a contribution of cells of medullary origin to the primordia of the sympathetic trunks via the ventral spinal nerve roots were corroborated. Cells were also traced from these primordia into the primordia of the prevertebral plexuses, but not into the plexuses which are functionally related to the vagi, viz.: the cardiac, pulmonary and enteric plexuses. On the contrary, the cells composing the primordia of the latter plexuses were traced distally along the vagi and their branches. This finding was corroborated by Abel (1912) in embryos of the chick, and by Stewart (1920) in embryos of the rat. The primordia of the autonomic ganglia in the head, according to the writer's (1920) observations, include both cells which are displaced distally along the nerves which convey the preganglionic fibers to the several ganglia respectively and cells which advance peripherally along the respective divisions of the trigeminal nerve.

Among the more recent investigators whose findings support the theory that the primordia of the sympathetic trunks are composed at least in part of cells derived from the neural tube via the ventral spinal nerve roots may be mentioned Ganfini (1911-1918), Rau and Johnson (1923) and Uchida (1927). Uchida, whose observations were based on embryos of reptiles (*Trigonocephalus*), birds (chick) and mammals (cat, dog, mouse, pig, calf), also concluded, on the basis of his findings, that the cardiac, pulmonary, and enteric plexuses in the esophagus and stomach contain mainly cells which are displaced distally along the vagi, but the enteric plexuses in the intestine first contain cells of sympathetic origin and later also receive cells of vagus origin.

Contrary to nearly all the more recent investigators in this field, E. Müller (1920) and Müller and Ingvar (1923) opposed the theory that cells of medullary origin are displaced into the sympathetic primordia, and supported the older theory that the primordia of the sympathetic trunks include only cells which are derived from the spinal ganglia or neural crests.

EMBRYOLOGICAL DATA.¹

Sympathetic Trunks.—The primordia of the ganglia of the sympathetic trunks appear earliest in the lower thoracic and upper abdominal regions. They are composed of aggregates of cells of nervous origin lying along the dorsolateral aspects of the aorta. The cells of nervous origin in these early primordia are somewhat scattered and may be differentiated from the cells of the mesenchyme by the somewhat larger size and more intense staining reaction of the nucleus (Fig. 17). Such aggregates of cells may be observed from the lower cervical to the sacral region in human embryos 6 mm. in



FIG. 16.—Transverse section through the thoracic region of a human embryo 7 mm. in length (No. 617, Carnegie Embryological Collection). *Sy.*, sympathetic trunks; *Oe.*, esophagus.

length. They are arranged segmentally, but by reason of the marked curvature of the embryo, they lie so close together that they constitute a continuous column of loosely aggregated cells. This condition obtains until the embryos have attained a length of 9 to 10 mm., when the sympathetic primordia are present from the upper cervical to the sacral region. The segmental character of the sympathetic primordia gradually becomes apparent, as development advances, and the cell aggregates become connected by

¹ The following descriptive account of the development of the autonomic nervous system is based mainly on an investigation carried out by the writer (1920) on preparations of human embryos included in the Carnegie Embryological Collection, made available through the courtesy of Dr. G. L. Streeter, Director of the Department of Embryology, Carnegie Institution of Washington.

longitudinal fibers. In the cervical and upper thoracic segments the sympathetic primordia lie along the dorsolateral aspects of the descending aortæ and in close proximity to the latter. The position of these primordia seems to be determined, at least in part, by the position of the paired descending aortæ. Inasmuch as these vessels lie at an appreciable distance from the median plane and converge toward the unpaired dorsal aorta, the sympathetic trunks lie farther from the median plane in the cervical and upper thoracic segments than in the lower thoracic and lumbar segments.

The primordia of the ganglia of the sympathetic trunks are apparent before the fibers of the communicating rami can be traced into them in material prepared by the ordinary methods. In preparations of human embryos 7 mm. and over in length, the fibers of

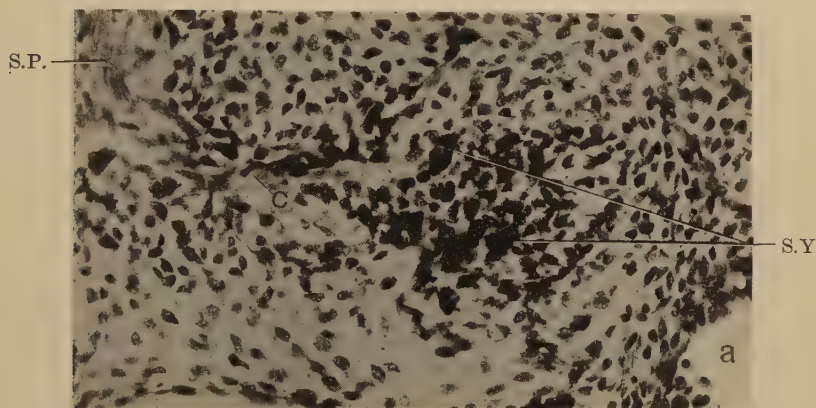


FIG. 17.—Transverse section through lower thoracic region of a human embryo 7 mm. in length, showing spinal nerve and sympathetic trunk. *a*, aorta; *C*, communicating ramus; *S.P.*, spinal nerve; *S.Y.*, sympathetic trunk.

the communicating rami extend into the sympathetic primordia throughout the greater part of the thorax and abdomen (Fig. 17). In preparations of embryos which are somewhat farther advanced, fibers tend ventralward from the primordia of the sympathetic trunks and enter the primordia of the ganglia of the prevertebral plexuses which are represented by scattered aggregates of cells along the ventrolateral aspects of the abdominal aorta (Fig. 18). These primordia arise by the ventral displacement of cells from the primordia of the sympathetic trunks.

The majority of the cells in the sympathetic primordia in early embryos are identical in appearance with the cells in the spinal ganglia and the indifferent cells in the mantle layer in the neural tube. Cells of the same character are present in the paths of the dorsal and ventral nerve roots and communicating rami. Occasion-

ally an individual cell, the nucleus of which lies partly within and partly without the external limiting membrane, may be observed in a ventral nerve root. Cells in this position obviously are in the process of emerging from the neural tube. Likewise, cells apparently become separated from the distal ends of the spinal ganglia and advance along the dorsal nerve root. Since the cells of medullary and spinal ganglion origin appear identical in early embryos, it is impossible to distinguish between the cells derived from those two sources distal to the junction of the dorsal and ventral nerve roots. The evidence at hand favors the assumption that cells from both these sources enter the sympathetic primordia.

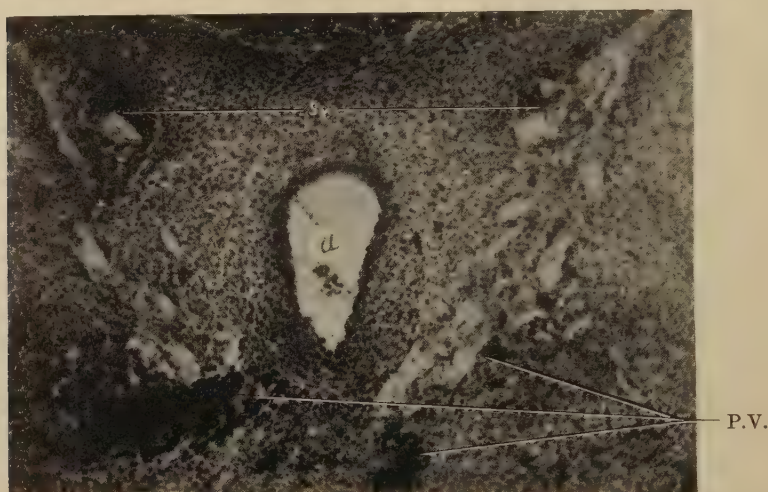


FIG. 18.—Transverse section through the abdominal region of a human embryo 10.1 mm. in length, showing primordia of sympathetic trunks and prevertebral plexuses. *A*, aorta; *P,V.*, prevertebral plexuses; *Sy.*, sympathetic trunks.

According to the writer's observations on human and other vertebrate embryos, cells of cerebrospinal origin are present in the sympathetic primordia before fibers of the communicating rami can be traced into these locations in material prepared by the ordinary methods. Certain other investigators have also expressed the opinion that many of the cells which enter the sympathetic primordia migrate peripherally in advance of the growing nerve fibers. Streeter (1912) emphasized the early migration of the cells into the sympathetic primordia in human embryos. He expressed the opinion that the majority of the cells which enter the primordia of the ganglia of the sympathetic trunks advance toward the aorta before fibers are present in the communicating rami; consequently, he described the communicating rami in early human embryos as

cellular strands. Ganfini (1917) also described the communicating rami in early mammalian embryos (guinea-pig, pig) as cellular structures. That the distal portions of growing nerve fibers are not brought out clearly by the ordinary processes of staining is well known. It may be assumed, therefore, that fibers of the communicating rami extend well into the sympathetic primordia somewhat earlier than the recorded data seem to indicate. Nevertheless, the earliest cells probably enter the primordia of the sympathetic trunks somewhat in advance of the growing nerve fibers.

In preparations of human embryos, 9 to 10 mm. in length, cells of cerebrospinal origin are still abundant in the spinal nerve trunks and communicating rami, indicating that the peripheral displacement of these cells is still going on. It probably does not continue much beyond the stage of embryos 11 or 12 mm. in length. The cells in the sympathetic primordia are also more numerous and are arranged more compactly than in the earlier embryos. Mitotic figures in the sympathetic primordia also indicate that the cells increase in number by local proliferation.

The primordia of the sympathetic trunks arise somewhat later in the cervical than in the thoracic region. This fact was noted by all the earlier investigators who made special mention of the development of the cervical portion of the sympathetic trunks in the embryos of the higher vertebrates. Some of them also observed that these primordia gradually extend cephalad from the upper thoracic level as continuous columns of cells until they reach the upper cervical segments. Yet, it was quite generally assumed that cells are contributed to the cervical sympathetic ganglia via all the cervical nerves, although these nerves have no white communicating rami. According to Ganfini (1917), cellular communicating rami extend from the cervical spinal nerves, in mammalian (guinea-pig, pig) embryos, toward the primordia of the sympathetic trunks through which cells advance into the latter. He maintained that these cellular rami persist for a short time and then disappear, after which there are no connections between the cervical spinal nerves, except the last, and the sympathetic trunks until the gray communicating rami arise. The writer was unable to substantiate these observations of Ganfini either in embryos of the pig or human embryos. Nor could he obtain any evidence that cells enter the primordia of the cervical sympathetic ganglia via the cervical spinal nerves. In both human and pig embryos the primordia of the sympathetic trunks grow cephalad from the lower cervical region both by the displacement of cells along the dorsal aspects of the descending aortæ and cell proliferation. These primordia do not appear segmented in early embryos, but remain continuous cell columns until segmentation of these columns takes place, resulting in the formation of the cervical sympathetic ganglia.

Uchida (1927) emphasized the close proximity of the superior cervical sympathetic to the vagus ganglia in mammalian embryos. He also described anastomosis of these ganglia, and expressed the opinion that cells of vagus origin are contributed to the cervical sympathetic ganglia. According to the writer's observations, the approximation of the superior cervical sympathetic and vagus ganglia occurs relatively late in their histogenesis. Although a contribution of cells of vagus origin is not precluded, it seems improbable that cells from this source play an important part in the development of the cervical sympathetic ganglia.

The segmental character of the sympathetic trunks is apparent throughout the greater part of their extent in human embryos 10 mm. in length. The ganglionic primordia are more compact at this stage than in the earlier stages, but some cells of nervous origin still remain somewhat scattered and, although the ganglionic masses in adjacent segments are connected by longitudinal fibers, these connecting rami are nowhere free from cells. As the curvature of the embryo becomes less marked, with advancing development, the ganglia of the sympathetic trunks become more widely separated and more sharply delimited. In human embryos, 15 mm. in length, the segmental character of the sympathetic trunks is well marked below the cervical region. The segmentation of the cervical portion which results in the cervical sympathetic ganglia is also well advanced. Fibers may now be traced cephalad from the superior cervical ganglia along the internal carotid arteries. In embryos, 20 to 22 mm. in length, the ganglia of the sympathetic trunks have taken definite form and are sharply delimited, the fibrous rami connecting them with each other are relatively free from cells, and the trunks have assumed a definite relationship to the vertebral condensations.

Prevertebral Plexuses.—The primordia of the ganglia of the prevertebral plexuses arise along the ventrolateral aspects of the abdominal aorta. In the upper abdominal region of human embryos, 6 mm. in length, cells may be traced in small numbers from the primordia of the ganglia of the sympathetic trunks ventralward along the lateral aspects of the aorta. The primordia of the ganglia of the sympathetic trunks in this region are not sharply delimited ventrally, but cells apparently become detached from them and advance ventralward into the primordia of the prevertebral ganglia. In embryos which are somewhat farther advanced fibers may also be traced from the primordia of the thoracic sympathetic ganglia below the fourth or fifth thoracic segment toward the primordia of the prevertebral ganglia in the upper abdominal region. These are mainly fibers which join the sympathetic trunks through the communicating rami of the thoracic nerves and, continuing toward the prevertebral plexuses, give rise to the splanchnic

nerves. In human embryos, 10 mm. and over in length, the aggregates of cells which constitute the primordia of the prevertebral ganglia are conspicuous along the abdominal aorta. Some cells have already become displaced from these cell masses toward the primordia of the adrenal glands and along the renal arteries. The greatest accumulation of sympathetic cells ventral to the abdominal aorta occurs at the origin of the celiac artery. The several prevertebral plexuses are not yet clearly delimited. Neither can fibers be traced from these plexuses into the mesentery. The several prevertebral plexuses become more clearly delimited as development advances, and the ganglionic cell aggregates become more compact.

Chromaffin System.—The chromaffin system consists of the medullary portion of the adrenals and the paraganglionic bodies. The latter are aggregates of chromaffin cells related to the sympathetic ganglia and located mainly along the abdominal aorta. Human embryos exhibit a wide range of variation in the number of paraganglia and the quantity of chromaffin tissue outside the adrenal bodies (Zuckermandl, 1901). Much of the chromaffin tissue outside the adrenals undergoes retrogressive changes during post-natal life, but the paraganglia do not wholly disappear.

Leydig (1853) regarded the adrenal bodies as an integral part of the sympathetic nervous system. Balfour (1878) clearly differentiated the chromaffin tissue from the interrenal tissue in elasmobranch embryos, and showed that the former is derived from the sympathetic primordia. Wiesel (1901) and Whitehead (1903) concluded, on the basis of their studies of mammalian embryos, that the adrenal medulla is composed of cells which are displaced from the adjacent sympathetic primordia. On the basis of extensive observations and a review of the literature, Poll (1906) advanced the opinion that the chromaffin tissue is composed of cells derived from the sympathetic primordia in all the vertebrates. The majority of the more recent investigators, including Kohno (1925), da Costa (1926) and Iwanow (1925, 1927), also concurred in this opinion.

The cells destined to become chromaffin cells cannot be differentiated from the other cells of nervous origin in the sympathetic primordia in early embryos. They assume the characteristic appearance of chromaffin elements relatively late during embryonic development. According to Soulié (1903), the displacement of cells from the adjacent sympathetic primordia into the adrenal capsules begins in human embryos about 19 mm. in length. The differentiation of cells of sympathetic origin into chromaffin cells and the formation of chromaffin bodies outside the adrenals is initiated at a somewhat earlier stage. According to Iwanow (1927), chromaffinoblasts may be recognized in some human embryos, 11.5 mm. in length, although such cells may not appear in other embryos which are somewhat farther advanced. Well-organized

chromaffin bodies are not found in human embryos until they have attained a length of about 30 mm. The cells which make up the adrenal medulla, according to Iwanow, are derived in part directly from the adjacent sympathetic primordia and in part from the chromaffin bodies along the abdominal aorta.

Plexuses Related to the Vagi.—The cardiac and pulmonary plexuses and the enteric plexuses in the esophagus and stomach arise from primordia composed of cells of cerebrospinal origin which are displaced distally along the paths of the vagi. This conclusion was first based on a study of mammalian (pig) embryos (Kuntz, 1909) and confirmed later by the results of studies based on embryos of types of the other classes of vertebrates.

The vagus nerves in early human embryos, like the spinal nerves, contain cells of nervous origin. In favorable sections through the vagus roots continuous lines of cells of medullary origin may be observed extending from the wall of the hind-brain into these roots. In sagittal sections, lines of cells also extend from the distal ganglion on the vagus nerve into the nerve trunk. Cells identical in appearance with those in the ganglionic cell masses are also present in abundance in the more distal parts of the growing vagi. Vagus branches bearing small aggregates of such cells may also be traced toward the esophageal wall.

In embryos 6 mm. in length vagus branches may be traced to the stomach and for a short distance along its lesser curvature, toward the roots of the lungs, and toward the bulbar region of the heart. All these branches contain many cells of nervous origin. In embryos, 7 to 9 mm. in length, the pulmonary branches have reached the roots of the lungs and the cardiac branches may be traced close to the base of the heart. The latter branches are accompanied by numerous cells of nervous origin which tend to become aggregated near their growing tips and give rise to the primordia of the cardiac ganglia. The esophageal plexus is already well formed over the dorsal aspect of the heart and comes into close proximity to the walls of the atria. Vagus branches with their accompanying cell aggregates form a plexiform meshwork around the lower portion of the esophagus (Fig. 19). Below the bifurcation of the trachea, vagus branches containing cells of nervous origin may be traced into the roots of the lungs, where masses of these cells occur in proximity to the bronchi and pulmonary vessels (Fig. 20). These nervous complexes which constitute the primordia of the pulmonary plexuses are continuous with the esophageal plexus and with that portion of the cardiac plexus which is associated with the walls of the atria.

In human embryos, 7 to 9 mm. in length, many cells of vagus origin have advanced into the wall of the esophagus, but a definite concentric arrangement of these cells is not yet apparent. In

embryos, 10 mm. in length, vagus branches accompanied by migrant nerve cells may be traced along the wall of the stomach. Many of



FIG. 19.—Esophageal plexus in transverse section, human embryo 10.1 mm. in length
O, esophagus; OEP, cell masses in esophageal plexus; VB, vagus branches.

these cells penetrate the stomach wall with the terminal vagus branches and become incorporated in the primordia of the enteric



FIG. 20.—Esophageal and pulmonary plexuses in transverse section, human embryo 10.1 mm. in length. B, bronchus; O, esophagus; OEP, cell mass in esophageal plexus; PP, cell masses in pulmonary plexuses; VB, vagus branches.

plexuses. As development advances, the primordia of the enteric plexuses also become apparent in the intestine. As the cells of nervous origin in the wall of the digestive tube gradually become

more numerous, they become aggregated in minute ganglionic masses which assume a concentric arrangement in two layers constituting the primordia of the myenteric and submucous plexuses.

It is significant that no paths along which cells advance from the sympathetic trunks or prevertebral plexuses into the pulmonary, cardiac, and enteric plexuses in the more proximal divisions of the digestive tube are established during the early stages of development. Indeed, the early development of the latter plexuses goes on simultaneously with that of the sympathetic trunks and prevertebral plexuses. Sympathetic nerves grow into the plexuses related to the vagi later, but not until the great majority of the cells which enter their primordia are already present. The possibility that some cells may enter these plexuses via the sympathetic nerves which join them is not precluded.

According to the writer's observations, the primordia of the enteric plexuses in the small intestine are also composed mainly of cells of vagus origin. Abel (1912) also supported this view, on the basis of her findings in embryos of the chick. On the contrary, Uchida (1927) advanced certain data which he interpreted as indicating the displacement of cells from the sympathetic primordia into the walls of the intestine before cells of vagus origin have advanced far enough to reach the intestine. He concluded, on the basis of his findings, that the primordia of the enteric ganglia in the intestine are composed mainly of cells of sympathetic origin, and later also receive cells of vagus origin, although the primordia of the enteric ganglia in the esophagus and stomach are made up mainly of cells of vagus origin. In view of the similarity in the functional relationships of the enteric plexuses in the stomach and small intestine to the vagi, such a radical difference in the histogenetic relationships of these plexuses in these divisions of the digestive tube seems improbable. Our own findings, however, do not preclude a contribution of cells of sympathetic origin to the enteric plexuses in any part of the intestine, and strongly suggest such a contribution in its more distal parts. Further investigation of the histogenesis of the enteric plexuses in the intestine would be highly desirable.

The enteric plexuses in the hind-gut probably sustain a histogenetic relationship to the sacral nerves which is comparable to the histogenetic relationship of these plexuses in the proximal divisions of the digestive tube to the vagi. Exact data bearing on the rôle of the sacral nerves in the development of the enteric plexuses are not available. More exact knowledge regarding the developmental relationships of the enteric plexuses throughout the small and large intestine awaits the results of further investigation.

Cranial Autonomic Ganglia.—Ciliary Ganglion.—The primordium of the ciliary ganglion is composed of cells which are displaced distally along the oculomotor and ophthalmic nerves. The periph-

eral displacement of cells along the oculomotor nerve is not very apparent in early human embryos, but some cells apparently of nervous origin are present in the nerve trunk. In some embryos an aggregate of intensely staining cells could be observed on the oculomotor nerve at the site of the primordium of the ciliary ganglion before cells could be traced to this point from the ophthalmic nerve. The latter nerve has the appearance in early human embryos of a nerve along which cells are advancing distally. Continuous lines

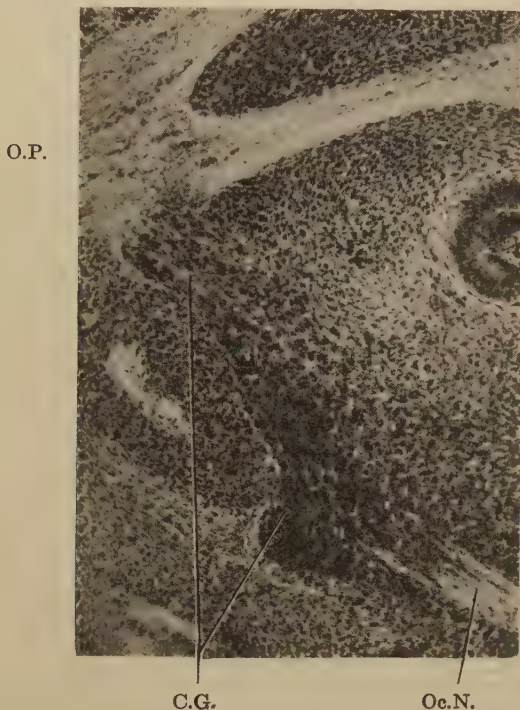


FIG. 21.—Sagittal section through primordium of ciliary ganglion, human embryo 14 mm. in length. *C.G.*, ciliary ganglion; *Oc.N.*, oculomotor nerve; *O.P.*, ophthalmic nerve.

of cells identical with the cells in the semilunar ganglion extend from this ganglion along the ophthalmic nerve. Cells also become aggregated very early in the path of this nerve at a point just proximal to the origin in the nasociliary ramus. This aggregate of cells gradually extends toward the oculomotor nerve until it becomes continuous with the cell aggregate on the latter nerve. The primordium of the ciliary ganglion now consists of a continuous mass of cells extending from the ophthalmic to the oculomotor nerve (Fig. 21). At this stage (14 mm.) nerve fibers may be

traced from the oculomotor nerve into the primordium of the ciliary ganglion. As development advances, this ganglionic cell mass gradually becomes separated from the ophthalmic nerve, but remains in contact with the oculomotor nerve until relatively late. The primordium of the ciliary ganglion in human embryos is relatively large. The great majority of the cells composing it are derived from the semilunar ganglion, but the aggregate of cells contributed via the oculomotor nerve is not insignificant. On the basis of these observations, the ciliary ganglion must be regarded as genetically related to both the oculomotor and ophthalmic nerves. This is in full accord with the findings of Carpenter (1906) in embryos of the chick, and Ganfini (1917) in embryos of various vertebrates. On the contrary, Broman (1911), Streeter (1912) and Stewart (1920) described the ciliary ganglion as derived exclusively from the semilunar ganglion.

Sphenopalatine Ganglion.—The primordium of the sphenopalatine ganglion arises at the growing tip of the greater superficial petrosal nerve as an aggregate of cells which are displaced distally along this nerve. It first becomes apparent in human embryos 10 to 11 mm. in length. The geniculate ganglion is not sharply delimited during early development. Cells apparently become separated from it and advance along the path of the greater superficial petrosal nerve. This nerve has the appearance, during early development, of a narrow migration pathway. It need not be assumed, however, that all the cells which are displaced along this nerve are derived from the geniculate ganglion. Many of them probably are cells of medullary origin.

The primordium of the sphenopalatine ganglion lies medial to the maxillary nerve, but not in contact with it. In embryos, 12 to 15 mm. in length, rami of the maxillary nerve accompanied by cells derived from the semilunar ganglion, may be traced into the sphenopalatine primordium. Probably the majority of the cells in this primordium advance into it via the greater superficial petrosal nerve, but it also receives cells from the semilunar ganglion via the maxillary nerve and its sphenopalatine rami. Ganfini (1917) recognized a contribution of cells to the sphenopalatine ganglion via the greater superficial petrosal nerve in embryos of the guinea-pig and pig, but did not regard it as sufficient to play a significant part in the development of this ganglion. On the contrary, Stewart (1920) maintained, on the basis of his observations on embryos of the pig and rat, that the primordium of the sphenopalatine ganglion contains only cells which are displaced distally along the greater superficial petrosal nerve.

Otic Ganglion.—The primordium of the otic ganglion arises at the growing tip of the lesser superficial petrosal nerve as an aggregate of cells which are displaced distally along this nerve. It is

first apparent in human embryos 9 to 10 mm. in length. In sagittal sections of embryos, 8 mm. in length, the tympanic ramus of the glossopharyngeal nerve may be traced to the level of the geniculate ganglion. Its fibers are accompanied by cells of nervous origin, giving it the appearance of an early migration path. The primordium of the otic ganglion may usually be recognized when this ramus has reached a point a little below the level of the semilunar ganglion. It increases in size rapidly and becomes elongated. Its upper pole soon extends above the lower level of the semilunar ganglion and lies in close proximity to this ganglion. During the

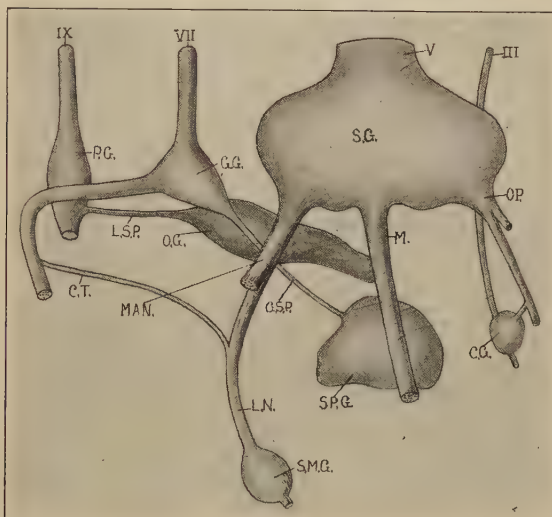


FIG. 22.—Diagrammatic reconstruction of the larger cranial autonomic ganglia and the nerves to which they are genetically related in a human embryo about 20 mm. in length. *C.G.*, ciliary ganglion; *C.T.*, chorda tympani; *G.G.*, geniculate ganglion; *G.S.P.*, greater superficial petrosal nerve; *L.N.*, lingual nerve; *L.S.P.*, lesser superficial petrosal nerve; *M.*, maxillary nerve; *MAN.*, mandibular nerve; *O.G.*, otic ganglion; *O.P.*, ophthalmic nerve; *P.G.*, petrosal ganglion; *S.M.G.*, submaxillary ganglion; *S.P.G.*, sphenopalatine ganglion.

early phases of its development the primordium of the otic ganglion is not connected with the semilunar ganglion, but in embryos 13 mm. and over in length it is apparent that cells derived from the semilunar ganglion become incorporated in the primordium of the otic ganglion. The otic ganglion now lies in contact with the proximal portion of the mandibular nerve. This nerve, like the other divisions of the trigeminal, contains numerous cells of cerebrospinal origin, some of which deviate from its course along the slender rami which join the otic ganglion. Inasmuch as the mandibular nerve has a motor as well as a sensory root, it is not improb-

able that a portion of the cells which advance distally along its course are derived directly from the hind-brain, but it is quite apparent that many of the cells of trigeminal origin which enter the otic ganglion are derived directly from the semilunar ganglion. Broman (1911) and Streeter (1912), who studied the development of the otic ganglion in human embryos, and Ganfini (1917), who studied it in embryos of the pig and guinea-pig, supported the theory that the cells which give rise to this ganglion are derived exclusively from the semilunar ganglion. On the contrary, Stewart (1920), who studied preparations of embryos of the pig and rat, maintained that the otic ganglion arises solely from cells which are displaced distally along the lesser superficial petrosal nerve.

Submaxillary Ganglion.—The primordium of the submaxillary ganglion arises in human embryos, 10 to 11 mm. in length, as an accumulation of cells in the path of the lingual division of the mandibular nerve. In view of the developmental relationship of the other cranial autonomic ganglia to the nerves which convey their preganglionic fibers, we should expect to find cells of facial origin displaced into the primordium of the submaxillary ganglion along the chorda tympani. The chorda tympani, however, does not join the lingual nerve until the primordium of the submaxillary ganglion has attained considerable size. It is quite probable that cells which advance from the facial nerve along the chorda tympani enter the primordium of the submaxillary ganglion during its later development, *i. e.*, after the junction of the chorda tympani with the lingual nerve is effected, but the cells which enter this primordium early are cells of trigeminal origin, some of which probably advance directly from the hind-brain along the motor root of the mandibular nerve. Obviously, the great majority of the cells which enter the submaxillary ganglion are of trigeminal origin. This is in full accord with the findings of Broman (1911) and Streeter (1912) in human embryos. Ganfini (1917) advanced the opinion, based on his findings in embryos of the pig and guinea-pig, that the submaxillary ganglion arises solely from cells of trigeminal origin. On the contrary, Stewart (1920) concluded that the submaxillary ganglion arises exclusively from cells which are displaced along the chorda tympani, although he admitted that by reason of the intimate relationship of the primordium of this ganglion with the lingual nerve, direct observations lend little support to this conclusion.

Sublingual and Lingual Ganglia.—The primordium of the sublingual ganglion arises as an accumulation of cells in the path of the lingual nerve somewhat distal to the primordium of the submaxillary ganglion. Cells of nervous origin also advance along the branches of the lingual nerve and give rise to small ganglionic masses in the tongue. These minute ganglia remain associated with the branches of the lingual nerve. Obviously, the cells which give rise to the

sublingual ganglion and the smaller ganglia in the tongue associated with the branches of the lingual nerve are derived from the same sources as those which give rise to the submaxillary ganglion.

Minute ganglia also occur in the posterior portion of the tongue. They are associated with the lingual ramus of the glossopharyngeal nerve and probably include only cells which are displaced distally along this nerve. As the glossopharyngeal nerve grows into the tongue, groups of cells accumulate near its growing extremity. Some of these cell groups remain closely associated with the nerve trunk; others give rise to minute ganglia throughout the portion of the tongue which is innervated by the glossopharyngeal nerve.

Histogenetic Relationships.—The conception that the cells which give rise to the ganglia of the sympathetic trunks and prevertebral plexuses are derived at least in part from the neural tube via the ventral roots of the spinal nerves represents a wide departure from the older teaching, but is in full accord with our present knowledge of the functional relationships of the sympathetic system. The neurons in the ganglia of the sympathetic trunks and prevertebral plexuses are commonly regarded as efferent in function. In the central nervous system efferent neurons arise mainly in the ventral or basal plate and afferent neurons mainly in the dorsal or alar plate; consequently, it is more logical to assume that the sympathetic neurons are derived from the ventral portion of the neural tube, which is a source of efferent neurons, than from the spinal ganglia or neural crest, which is essentially a source of afferent neurons. Yet, certain recent investigators, particularly E. Müller and Ingvar (1923), have maintained that the sympathetic primordia are composed of cells which are derived exclusively from the spinal ganglia or neural crests. They contended that no cells of medullary origin become displaced into the ventral roots of the spinal nerves.

The existence of cells of medullary origin in the ventral spinal nerve roots has been reported in embryos of all classes of vertebrates. The evidence that these cells are displaced from the ventral part of the neural tube via the ventral nerve roots is especially clear in elasmobranch embryos. Balfour (1877) described the early ventral nerve root in these embryos as "an elongate cellular structure with a wide attachment to the spinal cord." His illustrations indicate continuity of this cellular structure with the mantle layer in the wall of the neural tube. This condition is illustrated in Fig. 23, taken from a cross-section of an embryo of *Acanthius* in our collection. Continuous lines of cells extending from the mantle layer of the neural tube into the ventral nerve roots may also be observed occasionally in preparations of embryos of birds and mammals. This condition, as observed in preparations of an embryo of the chick, is illustrated in Fig. 24. Individual nuclei partly within and partly without the external limiting membrane in the

ventral nerve roots occur not uncommonly in preparations of embryos of all the higher vertebrates, including the human species.

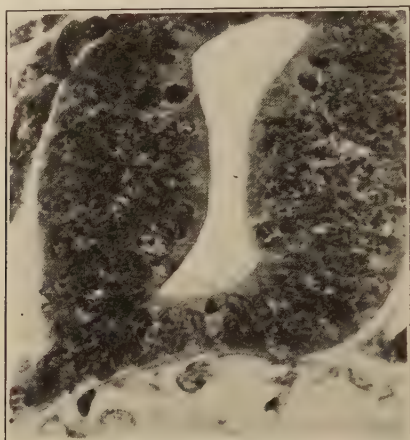


FIG. 23.—Section through the ventral root of a spinal nerve in an embryo of *Squalus acanthias*. A column of cells of medullary origin extends into the nerve root.

In an investigation undertaken to determine more exactly the rôle of cells of medullary origin in the development of the sympathetic ganglia, embryos of the chick were subjected to an opera-

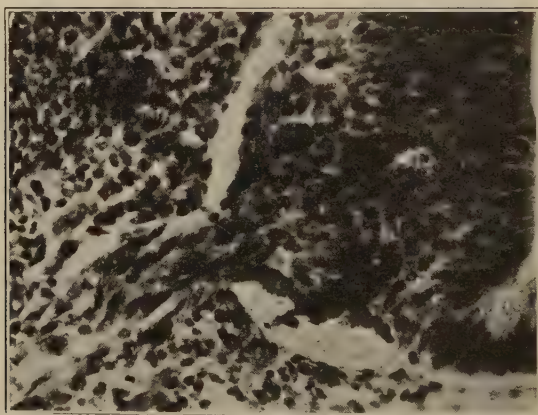


FIG. 24.—Section through the ventral root of a spinal nerve in an embryo of the chick about the close of the fourth day of incubation. Cells of medullary origin are present in the ventral nerve root.

tive procedure, before the close of the second day of incubation, by which a part or all of the nervous tissue was destroyed throughout

a series of segments. These embryos were killed about the close of the fifth day of incubation and prepared for study (Kuntz, 1922, 1923).

In some of these embryos, as became apparent on microscopic examination of the sections, the spinal ganglia and dorsal nerve roots were absent on one or both sides throughout a series of segments, while the ventral portion of the neural tube remained intact and the ventral nerve roots were apparently of normal size. In other embryos nearly all the nervous tissue was destroyed in a series of segments, leaving only a small ventral portion of the neural tube intact. In nearly all these cases ventral nerve roots were present, but diminished in size in proportion to the degree of destruction of the basal plate of the neural tube. Visceral rami were present wherever a part or all of the portion of the mantle layer which gives rise to the intermediolateral cell column remained intact, but absent wherever this portion of the mantle layer was completely destroyed. Preparations of embryos, in which all the nervous tissue was destroyed throughout a series of segments, showed no traces of spinal nerves in these segments.

An aggregate of cells representing the sympathetic primordium was present in every instance in which there was a ventral nerve root with a visceral ramus, even though there was no spinal ganglion or dorsal nerve root, but no sympathetic primordium was observed in any segment in which there was no visceral ramus, even though there was a small ventral nerve root, except in one instance in which very small sympathetic primordia were present in the upper thoracic segments in complete absence of spinal ganglia and neural tube in these segments. Obviously, some cells were displaced peripherally in the segments in question in this embryo before it was subjected to operation. Sections through the lower thoracic segments in the same embryo revealed no sympathetic primordia. Apparently, the peripheral displacement of cells of nervous origin is initiated earlier in the upper than in the lower thoracic segments. Most of the preparations used showed no evidence of the peripheral displacement of cells of neural crest origin before the operative procedure was carried out.

The experimental data at hand warrant the conclusion that the primordia of the ganglia of the sympathetic trunk may arise in complete absence of spinal ganglion or neural crest cells. Under these conditions, the cells composing the sympathetic primordia must be derived exclusively from the ventral part of the neural tube via the ventral spinal nerve roots. The fact that such primordia do not arise in segments in which the portion of the mantle layer which gives rise to the intermediolateral cell column is destroyed, even though a small ventral nerve root is present, suggests that the cells which enter the sympathetic primordia via

the ventral nerve roots, under normal conditions, are derived mainly from this portion of the neural tube.

That cells become displaced from the spinal ganglia into the sympathetic primordia, under normal conditions, cannot be doubted. Neither can the ultimate fate of the cells of medullary and ganglionic origin respectively, which enter the sympathetic primordia, be determined by the microscopic study of embryonic material. Froriep's opinion that the sympathetic neurons are derived mainly from cells of medullary origin was based on the assumptions that the sympathetic neurons are mainly efferent and that the basal plate of the neural tube is the chief source of efferent neurons. Inasmuch as many of the cells of nervous origin which advance peripherally become differentiated into neurilemma cells, the cells of spinal ganglion origin which become incorporated in the sympathetic primordia could readily be accounted for without assuming that they become differentiated into sympathetic neurons. The data available at present, however, do not warrant the conclusion that no cells of spinal ganglion origin become differentiated into sympathetic neurons. Precisely what part cells derived from the neural tube play in the development of the sympathetic ganglia must be regarded as an open question.

That the primordia of certain of the parasympathetic ganglia include both cells of medullary and neural crest origin is less apparent. The cells which are displaced from the wall of the hind-brain into the rootlets of the glossopharyngeal nerve cannot be traced with certainty beyond the petrosal ganglion along the lesser superficial petrosal nerve. Neither can cells of medullary origin in the rootlets of the facial nerve be traced beyond the geniculate ganglion along the greater superficial petrosal nerve. Neither can the cells which advance from the wall of the hind-brain into the vagus rootlets be traced beyond the ganglia on the vagus trunk. On the other hand, the existence of one or more ganglia on a nerve trunk does not preclude the possibility that cells of medullary origin may advance along the nerve distal to the ganglia. Consequently, cells derived from the wall of the hind-brain may advance along the lesser superficial petrosal and greater superficial petrosal nerves respectively into the otic and sphenopalatine ganglia and along the vagi into the pulmonary, cardiac, and enteric plexuses. The primordium of the ciliary ganglion clearly includes cells of both medullary and ganglionic origin. Since it is clear that cells of medullary origin enter the primordia of parts of the autonomic nervous system, there is no reason to assume that the primordia of any part of this system contain only cells of neural crest origin.

The conception of the development of the autonomic nervous system here set forth does not imply that all the cells which become differentiated into neurons in its ganglia actually migrate from the

cerebrospinal nervous system. In a critical study of the differentiation of nervous tissue in the central nervous system, Schaper (1897) pointed out that the cells which arise by the mitotic division of the "germinal" cells in the ependymal layer do not all become differentiated into neuroblasts. He described them as "indifferent" cells, some of which become differentiated into neurons and others into neuroglia cells. He also pointed out that in the higher vertebrates many of the indifferent cells retain the capacity for further propagation by mitotic division and give rise to daughter cells of the same indifferent type which may become differentiated either into neurons or supporting cells. The great majority of the cells of nervous origin which are displaced distally along the cranial and spinal nerves conforms to Schaper's description of the indifferent cells. In preparations of embryos which are sufficiently advanced in their development, a neuroblast may be observed occasionally along the path of migration, but the great majority of the cells which develop into neurons in the autonomic ganglia do not become differentiated into neuroblasts until they have entered the primordia of these ganglia. Many migrant cells apparently of the indifferent type do not become differentiated into neuroblasts, but give rise to neurilemma. In preparations of early embryos of the higher vertebrates mitotic figures occur not infrequently in both the nerve trunks and the sympathetic primordia. It may be assumed, therefore, that many of the cells which become differentiated into neurons in the autonomic ganglia arise by the mitotic division of migrant cells either before or after they have become incorporated in the primordia of these ganglia. Consequently, the neurons in the autonomic system may be regarded as homologous with the neurons in the cerebrospinal nervous system.

CHAPTER VI.

INNERVATION OF THE HEART.

EXTRINSIC NERVES OF THE HEART.

THE heart is innervated through the sympathetic cardiac nerves, the cardiac branches of the vagi, and the cardiac plexus. The sympathetic innervation of the heart includes the superior, middle and inferior cardiac nerves, arising from the superior, middle, and inferior cervical ganglia respectively, and several rami which arise from the sympathetic trunk below the inferior cervical ganglion. The latter were not included in the earlier accounts of the innervation of the mammalian heart. Perman (1924) described nerves passing from the sympathetic trunk as low as the fourth thoracic segment on the left and the sixth thoracic segment on the right side to the heart in the calf. Cannon *et al.* (1926) found that complete elimination of the cardiac accelerators in the cat, by extirpation of the sympathetic trunks, requires removal of the sympathetic ganglia as low as the sixth or seventh thoracic segments. According to Ionescu and Enachescu (1928), thoracic cardiac nerves are constant in man and arise from the second to the fifth thoracic segments of the sympathetic trunks. The several rami arising from the sympathetic trunk anastomose with each other to form one or more nerves which approach the heart without further anastomosis in some cases, and join the inferior cervical cardiac nerve or cardiac branches of the vagus in others. They commonly give rise to collateral branches to the esophagus, bronchi, lungs and thoracic aorta. The left side of the heart is more abundantly supplied by these nerves than the right, by reason of the fact that many of the fibers from the right side cross over and become distributed to the left side of the heart. They supply mainly the atria, but many of them also reach the ventricles. The vagus supply to the heart usually consists of three rami on either side. The superior cervical ramus arises from the vagus trunk just distal to the origin of the superior laryngeal nerve. The inferior cervical, the largest cardiac ramus of the vagus, usually arises from the recurrent nerve. The third, or thoracic cardiac ramus, arises from the vagus trunk within the thorax. The efferent components of the sympathetic cardiac nerves are postganglionic fibers which arise from cells located in the sympathetic ganglia from which the nerves arise. The corresponding preganglionic fibers are components of

the upper thoracic nerves down to and including the fifth. The efferent components of the vagus branches to the heart are pre-ganglionic fibers which terminate in synaptic relationship to ganglion cells in the cardiac plexus. A large percentage of the preganglionic

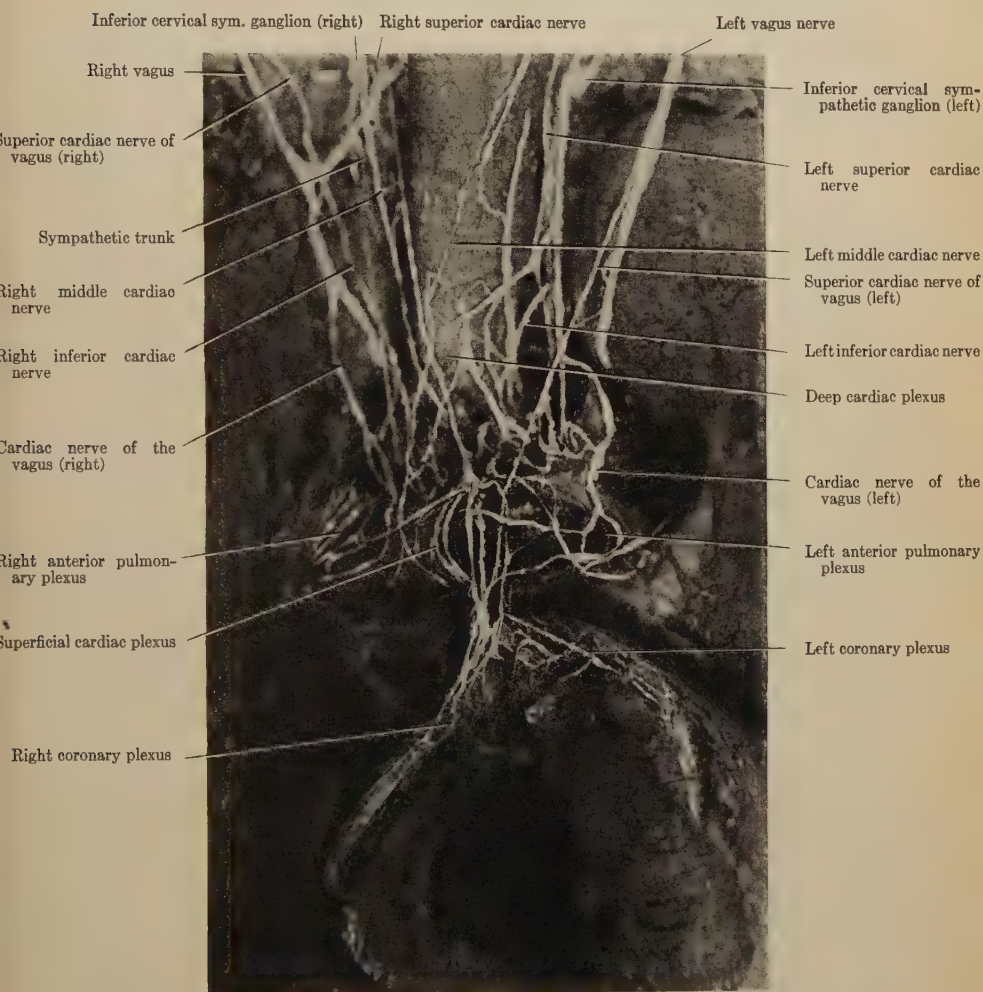


FIG. 25.—Photograph of a dissection of the nerves to the heart in the human cadaver. (By permission of Dr. J. D. Humber.)

vagus fibers (70 to 80 per cent, according to Glaser, 1924) is unmyelinated. As the vagus fibers approach the cardiac plexus they mingle with the cardiac sympathetic fibers, a large percentage of which is also unmyelinated. There are, therefore, no morphological

criteria by which the fibers of vagus and sympathetic origin can be certainly identified within the cardiac plexus.

Both the sympathetic cardiac nerves and the cardiac branches of the vagi also convey visceral afferent fibers. Those in the sympathetic nerves, like the corresponding preganglionic fibers, are components of the upper thoracic nerves. They are conveyed to the heart mainly through the middle and inferior cervical cardiac nerves. The thoracic cardiac nerves, according to Ionescu and Enachescu, also convey visceral afferent fibers. The superior cardiac nerve is probably devoid of afferent fibers, since no visceral afferent components traverse the cervical sympathetic trunk above the middle cervical ganglion (Ranson and Billingsley, 1918; Brünig and Stahl, 1924). Probably all the cardiac branches of the vagi contain visceral afferent components. The so-called depressor nerve is commonly regarded as a branch of the vagus, consisting mainly of afferent components which terminate in the proximal parts of the aorta and the adjacent cardiac wall (Köster and Tschermak, 1902). Certain investigators have questioned the vagus origin of this nerve and have advanced the opinion that it is essentially sympathetic. That the so-called depressor nerve is not uncommonly joined by a ramus from the inferior cervical sympathetic ganglion in the cat, has long been known (Kazem-Beck, 1888). A contribution of fibers from the sympathetic trunk to the so-called depressor nerve in man has not generally been recognized. On the basis of extensive clinical and anatomical data, Coffey, Brown, and Humber (1927) advanced the opinion that this nerve is sympathetic and has its origin in the superior cervical sympathetic ganglion. They were led to conclude, by the results of detailed anatomical studies in man and the cat, that the components of the depressor nerve join the vagus through the rami connecting the latter with the superior cervical sympathetic ganglion. Ionescu (1928) also regarded the so-called depressor nerve as one of the sympathetic nerves to the heart. Certain physiological data, however, seem to be incompatible with the view that the so-called depressor nerve is sympathetic; consequently, a final conclusion regarding the character of this nerve must await the results of further investigation.

THE CARDIAC PLEXUS.

Location and Distribution.—The cardiac plexus is situated at the base of the heart, and is composed of a superficial and a deep part. The superficial cardiac plexus lies superficial to the pericardium in the concavity of the aortic arch. It is made up largely by the left superior cardiac nerve and the inferior cervical cardiac branch of the left vagus. These nerves approach the heart by passing over the arch of the aorta and meet on the right side of the ligamentum

arteriosum. At this point there is usually a small ganglion, the cardiac ganglion of Wrisberg.

The deep cardiac plexus is situated behind the arch of the aorta and in part between the aorta and pulmonary veins. It is a large plexus, consisting of two lateral parts joined together by numerous fibrous communications. These two parts are quite unlike in com-

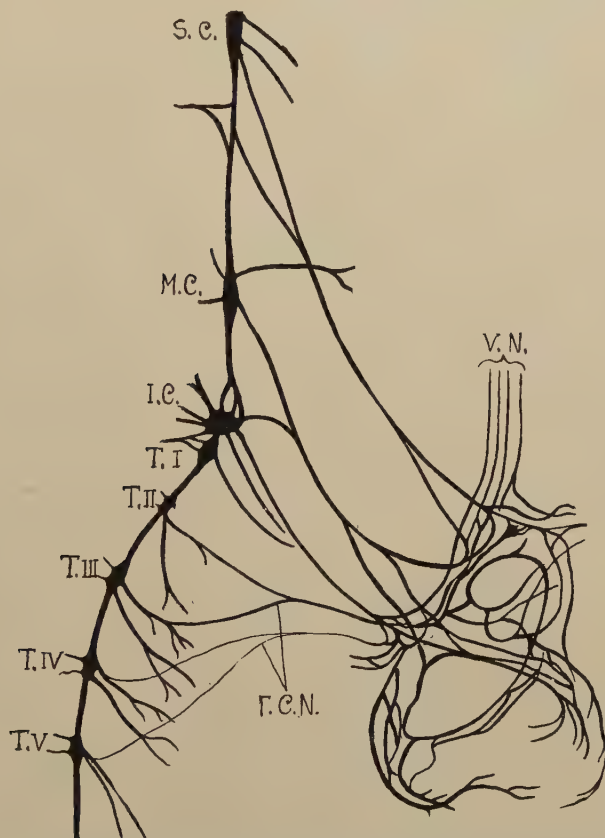


FIG. 26.—Diagram of sympathetic cardiac nerves and cardiac plexus. *I.C.*, inferior cervical sympathetic ganglion; *M.C.*, middle cervical sympathetic ganglion; *S.C.*, superior cervical sympathetic ganglion; *T.C.N.*, thoracic cardiac nerves; *V.N.*, cardiac branches of vagus nerves.

position and distribution. The right superior, middle, and inferior cardiac nerves and all the cardiac branches of the right vagus contribute to the right portion of this plexus. The left middle and inferior cardiac nerves and the superior and inferior cervical cardiac branches of the left vagus enter the left portion. It also receives communications from the superficial cardiac plexus. Indeed, all

the extrinsic nerves which contribute to the innervation of the heart, except the inferior cervical cardiac branch of the left vagus and the left superior sympathetic cardiac nerves, enter the deep cardiac plexus.

The superficial cardiac plexus sends branches of distribution along the pulmonary artery to join the anterior (right) coronary plexus. It also sends branches of communication along the left branch of the pulmonary artery to the anterior pulmonary plexus, and between the aortic arch and the bifurcation of the pulmonary artery to the left portion of the deep cardiac plexus.

The right half of the deep cardiac plexus contributes largely to the right or anterior coronary plexus. This plexus also receives fibers from the superficial cardiac plexus. It supplies the substance of the heart along the course of the right coronary artery. The right half of the deep cardiac plexus also contributes to the posterior coronary plexus and communicates with the right anterior pulmonary plexus. Reinforced by fibers from the superficial cardiac plexus, the left half of the deep cardiac plexus gives rise to the left or posterior coronary plexus which supplies the substance of the heart along the course of the left coronary artery. This portion of the deep cardiac plexus also contributes to the left anterior pulmonary plexus.

The deep cardiac plexus has been further subdivided, particularly by Worobiew and his associates. Worobiew (1917) described six more or less distinct plexuses beneath the epicardium of the human heart, viz.: anterior and posterior atrial, right and left anterior, and right and left posterior ventricular plexuses. Corresponding subdivisions of the deep cardiac plexus have been described more recently by Wolhynski (1928) in the calf, Anufriew (1928) in the cat and Schurawlew (1928) in the dog. According to these authors, the plexuses named above are constant components of the cardiac nerve supply, although they anastomose freely with each other and vary within relatively wide limits in different individuals.

Distribution of Cardiac Ganglia.—The intrinsic innervation of the heart has been studied by not a few investigators, but there is no general agreement regarding the number and distribution of nerve fibers in the several layers of the cardiac wall. These studies are beset with technical difficulties. Probably the most satisfactory preparations have been obtained by the use of the *intra vitam* methylene-blue technique. Silver impregnation methods have yielded satisfactory results in the hands of certain investigators. Differences in technique have played a large part in the interpretation of the histological findings.

Ganglia have been described in all parts of the heart in man and other mammals as well as lower vertebrates. The results of the most recent investigations, however, do not indicate so wide a

distribution of cardiac ganglia. Perman (1924), who investigated 30 human hearts, found numerous ganglia on the posterior surface of the atria and the roots of the great vessels. These ganglia, according to his findings, are always interpolated in the nerve trunks. He divided them into two groups: one, in proximity to the aorta and pulmonary artery and extending to the proximal ventricular wall; the other, on the posterior surface of the atrium and extending to the proximal part of the ventricle. The first group is associated with the nerves which pass ventral to the transverse sinus and supply the ventral surface of the heart; the other is associated with the nerves which pass behind the transverse sinus to supply the atria and greater part of the dorsal surface of the ventricles.

In a recent investigation of the hearts of a variety of vertebrates including the snake, rabbit, cat and dog, Woollard (1926) combined *intra vitam* methylene-blue staining and the process of clearing used in the Spalteholtz method. He was able, by means of this technique, to obtain transparent preparations of the superficial layers of the entire heart, including the visceral pericardium and a stratum of the underlying muscle. The larger elements were studied macroscopically; the finer elements microscopically in sections of small pieces. Ganglia were found in abundance on the anterior and posterior surfaces of the left atrium and extending to both auricular appendages. A large chain of ganglia was found extending along the interatrial septum. Several large ganglia were observed in the region of the atrio-ventricular sulcus. Ganglia were also found about the base of the pulmonary artery and for some distance along its course. None was found on the ventricular side of the atrio-ventricular sulcus, except in the heart of the snake, where collections of ganglia occur in the region of the posterior interven-tricular sulcus. Neither did Anufriew (1928) and Schurawlew (1928) observe ganglia in the ventricular walls in the cat and dog. In view of the distribution of cardiac ganglia reported by the more recent investigators, it probably is safe to conclude that ganglion cells occur only rarely, if at all, in the ventricular walls in the mammalian heart.

The intramural cardiac ganglia vary greatly in size. The larger ones can easily be seen with the naked eye in transparent preparations. The smaller ones can only be detected microscopically (Woollard). According to the recent findings of Francillon (1928) in an advanced human fetus, these ganglia contain 8 to 150 ganglion cells. They lie mainly in the subepicardial connective tissue. Although some lie deeper than others, neither Perman, Woollard, nor Francillon found any which could be regarded as intramuscular. The distribution of the intramural cardiac ganglia, as observed by Francillon, is illustrated in Figs. 27 and 28.

Neurons in the Cardiac Ganglia.—The neurons in the cardiac ganglia were described in detail by Dogiel (1899) and Michailow (1908). Dogiel divided them into three classes, viz.: a class made up of polygonal cells with from 3 to 10 short varicose dendrites and an unmyelinated axon which can often be traced into the muscle; a second class including cells with long dendrites which often extend for considerable distances from the cell body, and an axon which is often myelinated throughout a part of its course and

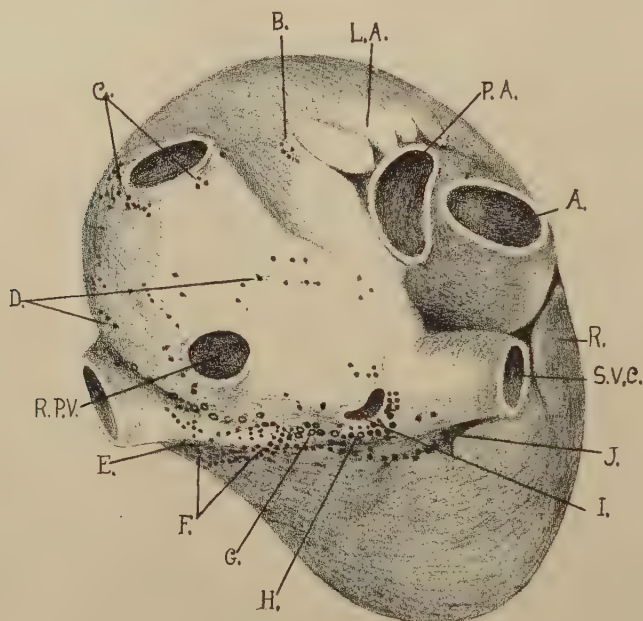


FIG. 27.—Distribution of ganglia at the base of the heart of a human fetus. *A.*, aorta; *B.*, ganglia in the sulcus between the left atrium and left auricle; *C.*, ganglia at the mouth of the pulmonary vein; *D.*, ganglia in the esophageal sulcus of the left atrium; *E.* and *F.*, ganglia in the caudal portion of the sulcus terminalis; *G.*, ganglia in the interatrial septum; *H.*, ganglia in the sulcus terminalis; *I.*, ganglia at the mouth of the right superior pulmonary vein; *J.*, superior group of ganglia in the sulcus terminalis; *L.A.*, left auricle; *R.P.V.*, right pulmonary vein; *S.V.C.*, superior vena cava. (Redrawn from Francillon.)

then loses its myelin sheath; and a third class including cells, some of whose dendrites interlace with dendrites of adjacent neurons. In addition to these classes, Michailow described cells which he called the rosette type. These cells are provided with a number of short dendrites arranged around the cell body so as to give the appearance of a rosette, and a single long dendrite which extends for a considerable distance from the cell body and terminates in a complicated end net which resembles very closely the terminal

structures of the myelinated fibers. These terminations lie quite free in the connective tissue. Woollard observed cells of this type only once or twice. He seemed inclined to regard the terminations of the long dendrites as sensory and suggested that these cells may be components of intracardial reflex arcs.

The neurons in the ganglion of Wrisberg were described by Müller (1910) as similar to the neurons in the ganglia of the sympathetic trunk. The majority of them are large, having a rounded or oval cell body and relatively large irregular dendrites which interlace freely with the dendrites of adjacent neurons.

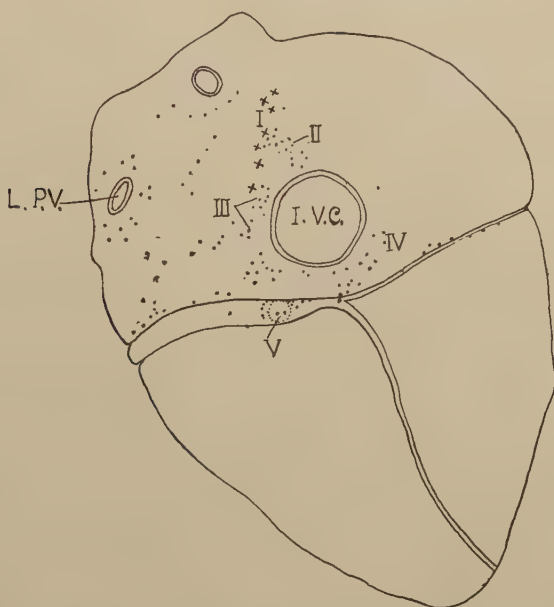


FIG. 28.—Distribution of ganglia on the diaphragmatic aspect of the heart of a human fetus. *I*, ganglia in the interatrial septum; *II*, ganglia in the sulcus terminalis; *III*, ganglia in the wall of the right atrium; *L.P.V.*, left pulmonary vein; *V*, projection of the mouth of the coronary sinus in the right atrium. (Redrawn from Francillon.)

Terminations of Incoming Fibers.—As the extrinsic nerves enter the cardiac plexus the fiber bundles gradually undergo changes in composition as they subdivide, intermingle with each other, and are intercepted by the cardiac ganglia. Since a large percentage of the fibers in the cardiac branches of the vagi is unmyelinated, and a considerable percentage of the postganglionic fibers in the cardiac nerves arising from the sympathetic trunks is myelinated, the presence or absence of myelin affords no criterion for the recognition of vagus and sympathetic fibers within the cardiac plexus. In

view of the intimate relationship of the cardiac ganglia to the mixed fiber bundles in the cardiac plexus, it has seemed probable to some investigators that both sympathetic and vagus fibers make synaptic connections in the cardiac ganglia. This view has not been confirmed by the results of physiological experiments.

Preganglionic fibers are in general larger than postganglionic fibers. This, however, does not afford a useful criterion, since many of the vagus fibers are actually smaller than the largest of the sympathetic fibers. There are no known morphological criteria by which pre- and postganglionic fibers can certainly be separated from each other in the terminal plexuses. Nevertheless, Woollard's observations afford some useful information bearing on this problem. He was able to recognize three distinct types of fibers in the nerves entering the cardiac plexus. Some of them are obviously myelinated and exhibit nodes of Ranvier. These may be regarded as visceral afferent. According to Woollard's findings, the depressor nerve includes fibers of this type. There are also large unmyelinated fibers with smooth contour. Such fibers can often be traced into the cardiac ganglia. The preganglionic character of these fibers is strongly suggested. On the other hand, fibers of this type may often be identified as arising from cells in the cardiac ganglia. These obviously are postganglionic, but when traced peripherally they soon lose their large and uniform character. As they approach their terminal distribution, they become exceedingly fine and exhibit the varicosities characteristic of the postganglionic fibers. The third group consists of varicose fibers of very much smaller caliber than the other two types. Fibers of this type were found throughout the cardiac plexus and in the incoming nerves. They probably are postganglionic. The fibers of this type are greatly reduced in numbers in the incoming nerves following extirpation of the stellate ganglia. This observation suggests that they are components of the sympathetic nerves. It does not, however, afford conclusive evidence that no components of the cardiac nerves arising from the sympathetic trunks make synaptic connections in the cardiac ganglia. The solution of this problem still awaits further physiological experimentation.

The modes of termination of the preganglionic fibers in the cardiac ganglia fall broadly into two types, viz.: the pericapsular and the pericellular. As the incoming fibers which form the pericapsular terminations break up into their terminal branches, the latter become varicose and are applied to the capsule of the nerve cell. In the pericellular terminations the terminal branches of the incoming fibers are applied to the cell bodies and dendrites. The cells with pericapsular terminations are usually stained less intensely, in methylene-blue preparations, than those with pericellular terminations. When the dendrites are relatively long the terminal branches

of the preganglionic fibers not infrequently twine around them throughout the greater part of their length. Not uncommonly preganglionic fibers may be seen to divide in various ways and to enter into synaptic relationship with a number of ganglion cells.

In view of the opinion of certain of the older investigators, that the cardiac ganglia belong wholly or in part to the sympathetic system, it has been suggested by some that the two types of synaptic connections referred to above may be associated with functional differences. On the basis of this theory, Woollard (1929) advanced the opinion that the fibers which form pericapsular endings belong to the sympathetic system, and those which form pericellular endings are components of the vagi.

As indicated above, physiological evidence does not support the theory that the cardiac ganglia contain both sympathetic and parasympathetic neurons. Neither is this theory warranted on morphological grounds. There is no direct morphological evidence that sympathetic fibers make synaptic connections with neurons in the cardiac ganglia. Neither could Woollard observe any alteration in the character or number of the pericapsular or pericellular terminations, nor any changes in any of the cells in the cardiac ganglia, following the removal of at least a large percentage of the sympathetic fibers by extirpation of the stellate ganglia. The best available evidence seems to warrant the conclusion that all the neurons in the cardiac ganglia belong to the parasympathetic system. This does not preclude the possibility of intrinsic cardiac reflexes, although there is no conclusive anatomical evidence for the existence of intracardiac reflex arcs.

Terminal Distribution of Nerve Fibers.—The distribution of nerve fibers in the cardiac wall and their modes of termination have been described by various investigators. That there is an abundant nerve supply to all parts of the heart is generally conceded, but there is no general agreement regarding the terminal structures in the cardiac musculature and the relative importance of the sympathetic and parasympathetic components.

There is an abundant plexus composed chiefly of unmyelinated fibers in the subepicardial tissue in all parts of the heart. The intracardiac ganglia are associated with this plexus. It is especially abundant in the areas of distribution of the ganglia and throughout the interatrial septum. Fiber bundles arising from this plexus penetrate the musculature and ramify throughout the myocardium, forming a loose meshwork between the fascicles of muscle cells and around them. There is also a relatively rich plexiform meshwork in the subendocardial tissue, from which offsets actually penetrate the endocardium. Both the parietal and visceral pericardium also contain a moderate number of relatively slender bundles of nerve fibers. According to Glaser (1924), the nerves in the pericardium

are made up largely of unmyelinated fibers, but also contain myelinated fibers in small numbers. He found no ganglion cells either in the parietal or visceral pericardium.

Regarding the distribution of fibers of sympathetic and vagus origin, Woollard found it possible, in transparent preparations of the hearts of cats and guinea-pigs, to define certain bundles along the posterior surface of the left atrium which neither bear ganglia nor receive fibers derived from ganglia in the cardiac plexus. These bundles probably are composed of sympathetic fibers which reach the ventricular wall without interruption in ganglia. In no instance was he able to trace fibers directly from the ganglia into the ventricles. On the other hand, both fibers of sympathetic origin and fibers derived from cardiac ganglia could be traced into the atrial walls.

As stated above, small varicose fibers are more abundant in the sympathetic cardiac nerves than in the cardiac branches of the vagi. The axons of the cardiac ganglion cells also become varicose toward their terminal ends; therefore, it becomes impossible to differentiate between the fibers of sympathetic and parasymphathetic origin in the terminal branches of the cardiac plexus. Yet, after degeneration of the severed sympathetic fibers, following extirpation of both stellate ganglia, the distribution and abundance of fibers is altered much more profoundly in the ventricles than in the atria. The intramuscular plexus, so prominent in Woollard's preparations of normal ventricular muscle, could hardly be demonstrated in preparations of the ventricles of the operated animals. The evidence put forward by Woollard strongly suggests that the atria and atrio-ventricular bundle are supplied by both sympathetic and parasymphathetic, and the ventricular muscle mainly by sympathetic fibers.

The anatomical data set forth above, in general, corroborate the results of the experimental studies of Cullis and Tribe (1913), who found that after section of the atrio-ventricular bundle in rabbits, vagus stimulation was without effect on the ventricles. On the basis of this result and the effect of atropin and pilocarpin, they concluded that the vagi supply no fibers to the ventricles and that the influence of vagus stimulation on the ventricles in the intact heart is exerted through the atrio-ventricular bundle. On the basis of results obtained by sympathetic stimulation and the use of adrenalin, they also advanced the opinion that the ventricles are abundantly supplied by sympathetic fibers. Wiggers and Katz (1920) also found, by the use of adrenalin, that the cardiac accelerators exert a direct influence on the ventricular musculature. On the basis of clinical studies, DeGraff and Weiss (1925) also concluded that the sympathetic cardiac nerves exercise considerable control over the ventricles in complete heart-block, whereas the vagi exert

only a slight influence. On the other hand, the vagus control of the atria in complete heart-block is essentially the same as in the normal heart.

As the fibers which supply the cardiac muscle approach their termination, they form delicate plexuses around the muscle fibers. Nearly all observers are in agreement on this point. They are not in agreement, however, regarding the terminal structure through which the nerve fiber is functionally connected with the cardiac muscle fiber. Certain investigators have described short terminal fibers arising from the intramuscular plexus which penetrate the muscle fibers. Others have described the terminal branches as ending on the surface of the muscle fibers in small end bulbs or end loops. Woollard claims to have demonstrated in methylene-blue preparation that the fibers of the intramuscular plexus ultimately penetrate the individual muscle cells and, running in the protoplasm of the muscle fibers, sometimes continue through the protoplasmic bridges into adjacent muscle fibers. Here and there along their course they give off small terminal twigs which terminate in small bulb-like enlargements or loops. Boeke (1925) previously described this type of termination in silver preparations of the heart of the tortoise.

Terminations of myelinated fibers, probably afferent in character, have been described in the heart in the region adjacent to the great vessels and in the proximal parts of these vessels. Within the heart they usually run independently or in small bundles and can be traced for some distance in favorable preparations. As the fiber approaches its destination, it gradually loses its myelin sheath. It usually extends for a short distance as a naked fiber, and then breaks up into numerous terminal filaments which may divide still further and finally terminate in bulbous enlargements. In the atrial wall these terminal structures lie in the subepicardial tissue and adjacent to the myocardium, but not actually on the muscle fibers. In the vessel walls they are situated in the adventitia, just superficial to the media (Woollard, 1926).

Delicate nervous plexuses are present also in the subepicardial and subendocardial tissue and the valves of the heart. These plexuses were not materially altered in Woollard's experimental animals following degeneration of the fibers interrupted by extirpation of both stellate ganglia. He, therefore, concluded that they are made up mainly of vagus fibers.

Innervation of the Coronary Arteries.—The coronary arteries exhibit a very abundant nerve supply. Large fibers of vagus origin terminate in the adventitia apparently without penetrating the media. Doubtless, these are afferent fibers. The media is richly supplied mainly by unmyelinated fibers of small caliber. Perhaps the majority of these are sympathetic, but fibers which arise in the

cardiac ganglia may also be traced directly to the coronary arteries (Woollard, 1926). These fibers terminate in relation to the individual muscle cells. This abundant nerve supply also extends along the branches of the coronary arteries at least as far as the arterioles.

Following extirpation of both stellate ganglia, Woollard found that a large percentage of the nerve fibers in the media of the coronary arteries and their larger branches underwent degeneration, but the supply to the smaller branches and arterioles was affected to a lesser degree. He concluded, therefore, that, while the coronary arteries are supplied by both sympathetic and parasympathetic nerves, the smaller branches and arterioles are innervated mainly by parasympathetic fibers. This fact, according to Woollard, may throw some light on the widely divergent results of physiological studies involving vasodilatation and vasoconstriction in the heart.

FUNCTIONAL RELATIONSHIPS OF THE CARDIAC NERVES.

Functions of Intrinsic Cardiac Nerves.—The functions of the intrinsic cardiac nervous system are not fully known. This system plays a rôle in the regulatory control which is exercised through the visceral components of the cerebrospinal nerves involved in the innervation of the heart, but to what extent the various activities of the heart depend on impulses emanating from the central nervous system is quite unknown. That rhythmic contraction of the heart is not dependent on the central nervous system is a fact of common knowledge. This, however, does not necessarily imply that rhythmic cardiac contraction may go on independently of the intrinsic cardiac nerves. Indeed, no essential rôle of this mechanism in rhythmic cardiac contraction has been demonstrated. The capacity for rhythmic contraction seems to be inherent in cardiac muscle.

Both afferent and efferent fiber terminations have been described in the heart. Various investigators have also maintained that the cardiac plexus includes a system of local reflex mechanisms. Morphological evidence for the existence of intracardiac reflex arcs must, however, be regarded as inconclusive. The fact that rhythmic contractions of the heart may continue after its connections with the central nervous system are severed, or even after it is removed from the body, does not warrant the assumption of an intrinsic reflex mechanism. It only shows that the isolated heart possesses automaticity, *i. e.*, the heart with its intrinsic nerves possesses the capacity to initiate and carry out the various phases of cardiac activity in the proper sequence to bring about coördinated contractions of its various parts.

The normal sequence of contraction of the cardiac musculature

probably involves differentiated conduction systems and graded differences in the degree of responsiveness to stimulation. These conduction systems are not nervous in the ordinary sense. As is well known, the cycle of contraction is initiated in the region adjacent to the entrance of the superior vena cava into the right atrium. The contraction phase also continues longest in this area. This area which corresponds to the sinus venosus in the more primitive vertebrate heart, may be regarded as the seat of the pacemakers for the entire heart.

One fact which stands out prominently is that the capacity for rhythmic contraction is not possessed by all parts of the cardiac musculature in equal degree. In the lower vertebrates it is extraordinarily developed in the sinus, but only to a moderate degree in the ventricle, and is hardly recognizable in the bulbus arteriosus. If, in a cold-blooded vertebrate, the sinus is functionally separated from the rest of the heart by a ligature around the sinu-atrial junction (Stannius' ligature), the sinus continues to beat, but the heart stops. After an interval the heart resumes beating, but at a slower rate. The new rhythm seems to be independent of that of the sinus. In like manner, if pressure is applied at the atrio-ventricular sulcus, as the cardiac tissue is gradually compressed, the ventricle, *i. e.*, the portion of the heart below the ligature, fails to beat as rapidly as the atria. This is known as partial heart-block. The degree of block may be indicated by the numerical expression, 2 to 1, 3 to 1, 4 to 1, etc., meaning that the sinus is beating twice, or three times or four times as quickly as the ventricle, as the case may be.

If the sinus is the seat of the pacemakers of the heart beat, *i. e.*, if it dominates the rhythmic contractions of the entire heart, as the best evidence available seems to indicate, the question arises as to how the impulse originated in this area is transmitted to the rest of the heart. A discussion of the physiological data bearing on this point is not within the scope of the present volume. It may be stated, however, that the balance of evidence favors the view that, at least in the cold-blooded heart, the propagation of the beat is myogenic and not neurogenic.

The conclusions drawn from the results of experimentation on the hearts of cold-blooded vertebrates cannot be assumed to be true for warm-blooded vertebrates without first establishing the structural relationships between cold-blooded and warm-blooded hearts. In all vertebrate embryos the heart arises as the so-called cardiac tube. The remains of this primitive tube are not apparent in the mammalian heart on superficial examination. It has been shown, however, by careful anatomical studies, that it exists in the mammalian heart in the specialized tissue which makes up the atrio-ventricular bundle. This tissue is histologically distinct from the rest

of the cardiac tissue and is disposed in a manner which suggests that it is the main pathway along which the heart beat is propagated.

At the upper end of this bundle in the mammalian heart is the atrio-ventricular node. This structure, situated near the posterior margin of the interatrial septum, consists of an aggregate of peculiar primitive cells and fibers. It is continued downward to the inter-ventricular septum. At a point a little in front of the attachment of the septal valve it bifurcates into right and left branches, which continue toward the apex of the heart just beneath the endocardium on each side of the interventricular septum. Ultimately, each branch gives rise to an intricate system of smaller branches which become reflected over the inner surface of the ventricles. These branches are made up of the so-called Purkinje fibers which ultimately terminate in close relationship with the papillary muscles.

As stated above, the cycle of contraction is initiated in the region at the mouths of the venæ cavæ. The evidence available strongly favors the conclusion that the heart beat actually originates in the sinu-atrial node. From this point it probably spreads through the muscular tissue of the atrial wall until it reaches the atrio-ventricular node. It is then transmitted to the ventricles along the atrio-ventricular bundle. This fact has been most clearly demonstrated by experiments involving heart-block. If, in the mammalian heart, a clamp is so arranged that it compresses practically nothing but the atrio-ventricular bundle, partial or complete heart-block may be produced at will. When moderate pressure is applied, ventricular contraction follows regularly every second, third or fourth atrial contraction. When the pressure is extreme, the rhythm of the ventricle becomes entirely independent of that of the atrium. When the pressure is relieved the heart-block usually disappears and the normal sequence of atrial and ventricular contractions is reestablished.

From the atrio-ventricular bundle, the impulse is propagated along its many branches which terminate in close association with the papillary muscles. These muscles are the first part of the ventricular musculature to contract. Obviously, this is significant in connection with the function of the papillary muscles in putting the chordæ tendinæ under tension, so as to keep the atrio-ventricular flaps from bulging into the atria when, at the beginning of ventricular contraction, high intraventricular pressure is brought to bear on their ventricular surfaces. After being initiated at these points in the ventricle, the wave of contraction seems to spread through the muscle at a fairly uniform rate.

Although the weight of evidence favors the conclusion that the heart beat is normally propagated along the atrio-ventricular bundle, it does not follow that the cardiac nerves play no part in this process. This tissue, like the rest of the cardiac musculature, is abundantly supplied by nerve fibers which, as shown by Woollard (1926), are

derived from both the sympathetic and parasympathetic supply. That conduction through the atrio-ventricular bundle is subject to alteration by impulses reaching it along the cardiac branches of the vagi, particularly those of the left vagus, is well known. Direct effects on the atrio-ventricular bundle of impulses originating in the cardiac plexus have not been demonstrated.

Function of Extrinsic Cardiac Nerves.—The control exercised through the extrinsic innervation of the heart on cardiac activities is primarily regulatory. In general, cardiac inhibition is a function of the vagi and cardiac acceleration a function of the sympathetic cardiac nerves. The extrinsic cardiac nerves also mediate impulses which modify the force of the heart beats and the conductivity of the cardiac muscle.

The results of recent physiological studies (Kohn, 1912; Robinson, 1913; Kohn and Lewis, 1913) have shown that in mammals the right vagus acts mainly on the sinu-atrial node and the left vagus on the atrio-ventricular bundle. This is also in agreement with the results of experiments carried out on cold-blooded animals. Stimulation of the right vagus always results in retardation and weakening of both the atrial and the ventricular beats. Stimulation of the left vagus sometimes has little influence on the atrial beat, although it may bring about a condition of partial heart-block, or, if the atrio-ventricular bundle is clamped, so that a condition of partial heart-block already exists, stimulation of the left vagus may result in complete heart-block. The left vagus also exerts a direct influence on the ventricles which affects the force of contraction rather than the rate.

The results of experimental studies carried out on the dog's heart by Bachmann (1923) indicate quite clearly that the various ganglion cell groups associated with the sinu-atrial junction are related to both vagi. Average computations based on the effects of the administration of nicotin and destruction of various parts of the area involved by a coagulating fluid show that the left vagus is distributed predominantly to the superior caval ganglia and the ganglia at the head of the sinu-atrial node, and the right vagus to the intercaval ganglia and those at the tail of the sinu-atrial node. In the majority of cases the ganglia in the coronary sinus receive only fibers of the left vagus. On the basis of these findings, it may be assumed that the greater inhibitory power of the right vagus noted above is directly related to its more extensive distribution to the ganglia associated with the sinu-atrial node. The percentile distribution of both vagus nerves to the ganglia associated with the sinu-atrial node, as pointed out by Bachmann, varies widely in different animals, the average order of dominance being sometimes reversed in individual cases.

Afferent impulses coming from any part of the body may influence

the heart through the vagi. Stimulation of the central end of any sensory nerve in mammals usually results in retardation of the heart beat, but some times elicits cardiac acceleration. Certain sensory nerves are more sensitive in this respect than others. Stimulation of the pulmonary branches of the vagi usually results in marked cardiac inhibition. Likewise, stimulation of trigeminal fibers through the mucosa of the upper respiratory passages, as by inhalation of irritating vapors, also brings about strong cardiac inhibition. Profound cardiac inhibition is also elicited by violent stimulation of the mesentery, as by a blow on the abdomen, or by irritation of the sensory nerves of the gastro-intestinal canal either mechanically or by reason of disease. Other illustrations of similar nature might readily be called to mind.

An increase in the blood pressure in the cephalic end of the carotid or vertebral arteries, under normal conditions, results in retardation of the heart-rate. According to Hering (1927), this is not brought about by a direct action of the cardio-inhibitory center, but through a reflex from the carotid sinus. This conclusion was confirmed by the work of Hymans (1928), who observed no retardation of the heart-rate in the dog due to increased blood pressure in the cephalic ends of the carotid arteries following denervation of the carotid sinus. An increase in blood pressure in the body circulation also results in reflex retardation of the heart.

Under certain conditions distention of a portion of the intestine reacts reflexly on the heart through its sympathetic innervation. Experimental data reported by Percy and Howard (1927) show that when the heart of a narcotized dog is poisoned by barium chloride or digitalis, distention of a segment of the intestine, by means of a balloon, elicits cardiac reflexes which result in increasing the T-lead and decreasing R at the end of the T-interval. These reflexes were not abolished by section of the vagi. Percy and Howard advanced the opinion that distention of the intestine may react upon the heart in a similar manner in the presence of any disease which damages this organ.

The effect of direct vagus stimulation on cardiac rhythm in man may be demonstrated by pressure on one of these nerves where it lies in front of the sixth cervical vertebra. Profound cardiac inhibition and even temporary loss of consciousness may be brought about in this way. In like manner, retardation of the heart-rate may be brought about by mechanical irritation of the nerve trunk, resulting from pressure caused by a tumor or an aneurism in the neck.

Retardation of the heart-rate in man may also be caused by direct stimulation of the vagus center, as by the pressure of a blood clot or tumor in the medulla, or by the reaction of this center to some unusual hormone in the blood. The vagus center is also

stimulated by a general increase in intracranial pressure. In the experiments of Anrep and Starling (1925) and Anrep and Segall (1926) a rise in general cerebral pressure caused slowing of the heart-rate. Likewise a variety of other conditions which result in direct stimulation of the vagus center causes temporary or prolonged retardation of the cardiac rate.

Cardiac acceleration is, in general, a function of the sympathetic cardiac nerves, but it does not involve the entire sympathetic supply. Herring (1924) could not elicit cardiac acceleration by stimulation of the cervical sympathetic trunk in mammals (dog, cat, rabbit, ape). Shiff and Brüning (1926) also failed to elicit acceleration of the heart beat in man by stimulation of the superior and middle sympathetic cardiac nerves. On the other hand, stimulation of the roots or communicating rami of the upper thoracic nerves, particularly those of the second and third, or the post-ganglionic fibers running from the stellate ganglion to the heart always results in cardiac acceleration. The accelerator fibers probably are conveyed to the heart mainly in the inferior cardiac nerves, but the thoracic cardiac nerves also contain accelerator fibers (Cannon *et al.*, 1926). In a recent clinical case, Adson (1928) reported no marked change in the cardiac rate following bilateral extirpation of the first and second thoracic segments of the sympathetic trunk. The balance between cardiac inhibition and acceleration probably was maintained in this case by the accelerator fibers in the thoracic cardiac nerves. In addition to bringing about cardiac acceleration, sympathetic stimulation also modifies the conductivity and contractile power of the cardiac musculature.

Sympathetic stimulation differs from vagus stimulation of the heart, in that a longer latent period elapses before it becomes effective. Likewise, the effect of sympathetic stimulation continues longer than that of vagus stimulation after the stimulus is withdrawn. Consequently, when the vagus and sympathetic nerves are stimulated simultaneously the vagus effect is observed first, and is usually followed, after the removal of the stimulus, by the sympathetic effect. If stimulation of both nerves is continued for a long time the vagus becomes fatigued and permits the sympathetic to become effective earlier than it would if the vagus alone were stimulated. The sympathetic influence, however, is never as strong as the vagus influence. Vagus and sympathetic nerves, therefore, are not antagonistic in the sense that the influence of the one is neutralized by that of the other, but when both are stimulated simultaneously the heart responds first to the vagus and later to the sympathetic. This difference in the response of the heart to vagus and sympathetic stimulation probably is an important factor in the normal functioning of the organ. It also lends support to the

theory that the vagus center is dominant in the regulatory control of the heart which is mediated through its extrinsic nerves.

Acceleration of the heart-rate may be brought about either by diminution of impulses from the vagus center or by increase in impulses from the augmentor center. Reflexes arising from changes in aortic pressure commonly influence the cardiac rate. In the experiments of Anrep and Segall (1926) a rise in aortic pressure regularly brought about retardation of the heart. Reflexes carried out through the augmentor center, which influence the heart-rate, can also be demonstrated under experimental conditions. If both vagi are cut and the peripheral end of one of them is stimulated sufficiently to keep the heart beating at almost its normal rate, stimulation of certain sensory nerves may elicit acceleration of the heart beat. Under normal conditions, however, reflex control of cardiac rhythm through the augmentor center is probably much less important than reflex control through the vagus center.

Afferent impulses arising in the heart and proximal portion of the aorta reach the central nervous system via both the vagus and sympathetic nerves. The afferent impulses conveyed from the heart and aorta through the vagi probably do not reach the threshold of consciousness, but elicit reflex vasomotor responses. Spiegel and Wassermann (1926), who carried out extensive animal experiments in which pain reactions were elicited by distention of a portion of the aorta isolated by a ligature at either end, were unable to obtain evidence that the vagi play any part in the conduction of impulses from the aorta which give rise to sensations of pain. That impulses conveyed from the heart and aorta through the visceral afferent components of the sympathetic cardiac nerves may give rise to sensations, even pain, is well known, although these nerves also play a part in reflex vasomotor control.

According to Ionescu, Enachescu and Teitel (1928), electrical stimulation of the central ends of the sympathetic cardiac nerves elicits vasomotor reflexes, changes in heart-rate, and pain reactions. They also elicited pain reactions by mechanical and chemical stimulation of the heart and aorta after section of the afferent fibers conveyed to the heart through the cervical cardiac nerves. On the basis of these results, they concluded that the thoracic cardiac nerves, like the inferior and middle cervical sympathetic nerves to the heart, contain both accelerator and sensory fibers.

As stated above, the existence of afferent components in the superior sympathetic cardiac nerve and the upper portion of the cervical sympathetic trunk has not been demonstrated anatomically. Yet, certain experimental and clinical observations (Coffey, Brown, and Humber, 1927) indicate that manipulation of the superior cardiac nerve and superior cervical sympathetic ganglion or grasping them with forceps, during an operative procedure, may give

rise to pain. These observations seem to be at variance with the anatomical evidence against the occurrence of afferent fibers in the superior cervical portion of the sympathetic trunk, and call for further investigation of this portion of the sympathetic system.

According to the current physiological teaching, the so-called depressor nerve plays an important rôle in the regulatory control of the heart through its influence on both the cardio-inhibitory and vasomotor centers. It is assumed, on the basis of physiological evidence, that whenever the blood pressure rises above its normal limits the depressor fibers are stimulated, probably by the mechanical effect of the increased intracardiac pressure, and convey impulses to the medulla which tend to bring about reflex inhibition of the heart through the vagus center, and inhibition of vascular tonus through the vasoconstrictor center. In view of the anatomical evidence in support of the contention that the so-called depressor nerve is a sympathetic nerve, having its origin in the superior cervical sympathetic ganglion, the physiological relationships of this nerve also require further investigation.

ADDENDA.—Since this chapter was written, the existence of thoracic sympathetic cardiac nerves was confirmed in human cadavers in these laboratories. Mr. A. Morehouse, working under my supervision, traced nerves from the second, third and fourth thoracic ganglia of the sympathetic trunk on both sides into the cardiac plexus. In some instances a nerve arising from the fifth thoracic ganglion, particularly on the right side, also contributes some fibers to the cardiac plexus. The thoracic cardiac nerves are made up mainly of sympathetic fibers, but also contain some large myelinated fibers which probably are general visceral afferent components of the thoracic nerves.

CHAPTER VII.

INNERVATION OF THE BLOOD VESSELS.

ANATOMY OF THE NERVES OF THE BLOOD VESSELS.

Source of the Nerve Supply.—The nerve supply to the blood vessels includes both efferent and afferent components. The efferent component includes both vasoconstrictor and vasodilator fibers. The former are sympathetic; the latter are quite generally regarded as parasympathetic, but their anatomical relationships to the peripheral blood vessels are not fully known. Neither is it known to what extent the peripheral vessels are supplied by vasodilator fibers. The afferent fibers distributed to the blood vessels are components of the sensory cerebrospinal nerve roots.

The large blood vessels of the trunk, *e. g.*, the aorta and inferior vena cava, are supplied quite directly by the autonomic nerves nearest them. In the thorax these vessels receive fibers directly from the sympathetic trunks and the cardiac plexus. In the abdomen they are supplied by rami from the plexuses along the aorta. The arteries and veins supplying the abdominal organs are in the main innervated in the same manner. The vessels in the neck and head derive their innervation mainly from the cervical sympathetic ganglia. Rami from the inferior cervical and upper thoracic ganglia form a plexus on the vertebral artery which extends cephalad. Rami from the superior cervical ganglion form a rich plexus on the internal and a lesser plexus on the external carotid artery through which the sympathetic system is extended into the head. Not infrequently rami from the first thoracic and inferior cervical ganglia also join the common carotid artery. The peripheral vessels are supplied by sympathetic fibers which join them via the somatic nerves which lie in closest proximity to them.

Not a little evidence, mainly physiological in character, seems to indicate that parasympathetic fibers are conveyed to the peripheral blood vessels via the dorsal nerve roots. This theory was recently supported by Kuré *et al.* (1928), on the basis of experimental anatomical findings. They subjected animals (dogs) to unilateral section of the dorsal roots of the lower lumbar and upper sacral nerves proximal to the spinal ganglia and allowed them to live for relatively long periods following operation (eighty to ninety days or longer), after which the proximal portions of these dorsal roots were examined for intact nerve fibers. According to their findings,

numerous myelinated fibers of small caliber persisted in these nerve roots following degeneration of the central divisions of the fibers arising from the spinal ganglion cells: They regarded the small myelinated fibers which persisted as parasympathetic, and concluded, on the basis of histological findings in sections of the spinal cord, that they arise from small nerve cells in the gray matter at the base of the dorsal horn. They also advanced the opinion that these fibers effect synaptic connections in the spinal ganglia with special nerve cells, from which fine medullated fibers extend peripherally. If these anatomical findings are confirmed by the results of further investigation they will add materially to our knowledge of the anatomical relationships of peripheral parasympathetic fibers.

The data bearing on the afferent innervation of blood vessels are as yet meager. The existence of afferent fibers to the blood vessels can no longer be doubted, but the extent of the distribution of such fibers and their relationships to other nerve components are not definitely known.

The older anatomists were conversant with the fact that the peripheral arteries are joined by nerves along their course. Goering (1836) described the distribution of nerves to the peripheral blood vessels quite accurately. According to his accounts, the vascular rami arise from the nerve trunks at an acute angle, join the blood vessels, especially at points where the latter divide, and spread out in the superficial layers of the vessel walls. Frequently a nerve may pass an artery without giving off branches to it. The brachial artery, according to Goering, is supplied by branches of the median nerve, while the vessels in the forearm are supplied by branches of the nerves which accompany them. The femoral artery is supplied by branches of the femoral and saphenous nerves. The vessels of the leg, like those of the forearm, are supplied by branches of the nerves which accompany them. Frey (1874-1876) stated very definitely that the peripheral arteries and veins are supplied by branches of the nerve trunks which lie closest to them. He also stated that the cutaneous veins are supplied by branches of adjacent cutaneous nerves.

According to Kramer and Todd (1914), the subclavian and axillary arteries receive their nerve supply directly from the sympathetic trunk, but all the other arteries in the upper extremity are supplied by sympathetic fibers which are conveyed peripherally in the spinal nerves and are distributed to the various blood vessels at irregular intervals. The vessels in the more distal parts of the limbs, particularly those in the hands, are joined by branches of the adjacent nerves at more frequent intervals than those in the proximal parts of the limbs.

The plexus on the abdominal aorta gives rise to a subordinate plexus on the common iliac artery, from which some fibers extend

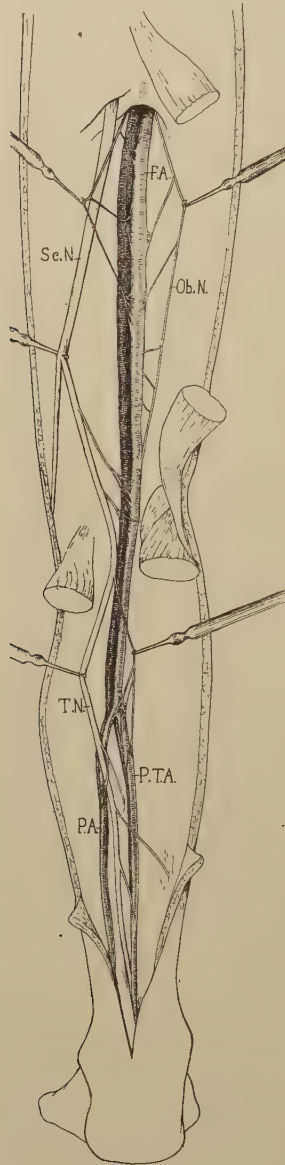


FIG. 29.—Drawing from a dissection of the lower extremity, showing the distribution of nerves to the large arteries. *F.A.*, femoral artery; *Ob.N.*, obturator nerve; *P.A.*, peroneal artery; *P.T.A.*, posterior tibial artery; *Sc.N.*, sciatic nerve; *T.N.*, tibial nerve. (Dissection by Mr. I. Levy.)

to the proximal portion of the femoral artery, but the more distal portions of the femoral artery and the other vessels of the lower extremity, like those of the upper extremity, are supplied by sympathetic fibers which are conveyed distally in the somatic nerves and are distributed to the vessels at irregular intervals (Potts, 1915). The distribution of nerves to the large arteries of the lower extremity, as observed in a careful dissection, is illustrated in Fig. 29.

In spite of the anatomical findings to the contrary, it has during recent years been maintained by some, mainly on the basis of observed results following periarterial sympathectomy, that long fibers, presumably arising from the plexuses on the aorta and its branches or the sympathetic trunk and extending distally in the adventitia of the peripheral arteries, play an important rôle in the innervation of the peripheral portions of the arteries, particularly in the lower extremities.

In a recent study of the extrinsic innervation of the vessels of the extremities, Hirsch (1925) employed minute dissection under moderate magnification, following silver impregnation of the nerves. The results of this study do not support the theory that long fibers derived from the aortic plexus accompany the peripheral arteries in any considerable numbers, but show clearly that the peripheral vessels are supplied by rami from the adjacent nerves at intervals all along their course. He was unable to find a plexus even on the common iliac artery which might be regarded as an extension of the plexus on the aorta. He regularly found but few fibers extending along the common iliac artery from the aortic plexus. Only a minor portion of these fibers become definitely related to the artery. As soon as the genito-femoral nerve comes into close proximity to the external iliac artery, it supplies branches to the latter. The femoral artery, as stated by Goering, is supplied mainly by branches of the femoral and saphenous nerves. Fiber bundles extending along the external iliac artery from the plexus on the common iliac could not be demonstrated. Hirsch properly maintained that if long fibers extending along the course of the artery were present in sufficient numbers to play an appreciable rôle in the innervation of the femoral artery and its widely distributed branches, there would be no difficulty by the method employed in detecting their presence.

The subclavian and the proximal part of the axillary artery are commonly supplied by fibers derived directly from the sympathetic trunk. According to Hirsch, the axillary and the proximal part of the brachial artery also receive fibers from the brachial plexus. Farther distally the brachial artery is supplied by branches of the several nerves which lie in proximity to it. In the upper part of the arm it is supplied mainly by branches of the radial and cutaneous nerves of the forearm. The distal half of the brachial artery is

supplied mainly by branches of the median nerve. The musculocutaneous nerve does not regularly supply branches to the brachial artery. The ulnar nerve occasionally supplies a few branches to its middle and distal parts.

The findings of Hirsch show clearly that the number of branches joining the vessels of the extremities from adjacent nerves is far greater and the total extrinsic nerve supply of these vessels is far richer than has been generally assumed. Many of the smaller nerves which join these vessels are so delicate that they cannot be detected by the ordinary methods of dissection. These finer rami are regularly imbedded in connective tissue. In general, they run nearly parallel with each other from the nerve trunk to the vessel, but not infrequently they exhibit more or less complex intercommunications with each other. As they enter the adventitia, some of their fibers become immediately incorporated in the adventitial plexus, while others pass through the adventitia quite directly and enter the media or, passing through only the superficial layers of the adventitia, ramify in its deeper layers.

In view of the fact that the peripheral nerves supply branches to the vessels of the extremities at intervals throughout their entire course, and no large longitudinal fiber bundles can be demonstrated along the course of the vessels, it is entirely obvious that these vessels receive the major portion of their nerve supply directly from the peripheral nerves. The branches supplied to the arteries contain both myelinated and unmyelinated fibers. There is reason to believe, on physiological grounds, that the purely vascular rami contain mainly sympathetic and dorsal root fibers. The exact sources of these fibers and the presence or absence of long fibers along the course of the vessels can best be determined by experimental anatomical methods.

In a recent experimental investigation carried out under my supervision, Kerper (1927) studied the several components of the nerve supply to the arteries of the extremities. In one series of experimental animals (dogs) he isolated the sympathetic nerve supply to a limb by section of both roots of the spinal nerves between the spinal ganglia and the communicating rami. In the case of the fore limb, the roots of the fifth, sixth, seventh and eighth cervical and first thoracic nerves were cut, leaving the communicating rami intact. In the case of the hind limb, the roots of the spinal nerves entering the lumbosacral plexus were cut, leaving the gray communicating rami intact. In another series of animals the sympathetic nerve supply was eliminated, leaving the spinal nerve roots intact. This was accomplished, in the case of the fore limb, by extirpation of the stellate ganglion, and in the case of the hind limb by extirpation of the sympathetic trunk from the fourth lumbar to the first sacral ganglion inclusive. In still another series of animals,

the brachial and femoral arteries were ligated and divided unilaterally. In a few cases this was done in addition to sympathetic extirpation. All the animals were allowed to live long enough, following operation (five weeks or longer), to insure complete degeneration of the interrupted nerve fibers. Segments of the arteries were then prepared by the pyridin-silver method and sectioned.

Following degeneration of the spinal nerve fibers, leaving the sympathetic innervation intact, nerve fibers were still present both in the adventitia and media of the arteries. The larger fibers

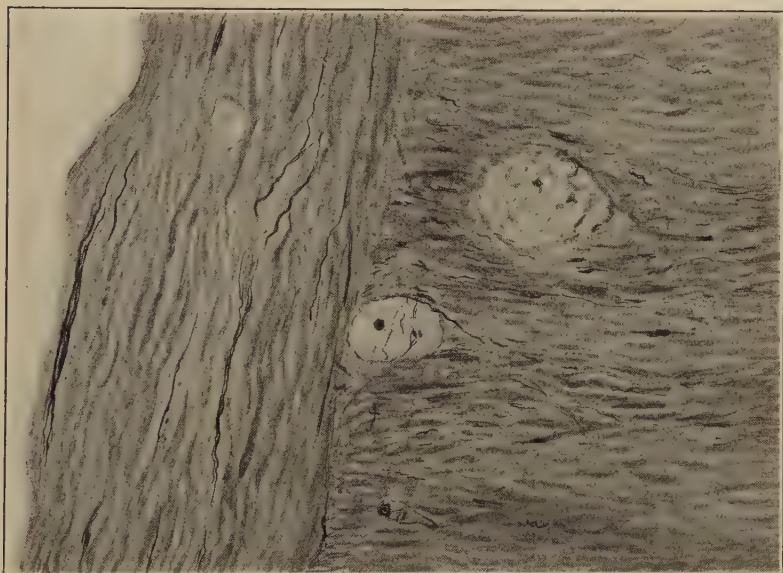


FIG. 30.—Drawing from a longitudinal section of the radial artery of a dog after degeneration of the spinal-nerve fibers following section of the dorsal and ventral nerve roots distal to the spinal ganglia, showing the distribution of sympathetic fibers in the adventitia and media. Nerve fibers indicated by black lines. (Kerper.)

normally present in the adventitia, however, were absent. The nerve supply in this layer was materially diminished. No marked diminution in the number of nerve fibers in the media was apparent (Fig. 30).

Extirpation of the stellate ganglion in the dog does not deprive the fore limb of all sympathetic fibers. Some are normally derived from the middle cervical ganglion, and not infrequently some join the brachial plexus from the second thoracic ganglion. Neither does extirpation of the sympathetic trunk from the fourth lumbar to the first sacral ganglion inclusive deprive the hind limb of all sympathetic fibers. Some are derived from the second and third

sacral ganglia. In selecting material from the animals which were subjected to sympathetic extirpation, however, segments of the arteries were taken from areas supplied by the spinal nerves which receive their gray rami from the portion of the sympathetic trunk which was extirpated. Following degeneration of the sympathetic fibers, leaving the spinal nerve roots intact, a goodly number of nerve fibers remained in the adventitia and some in the media (Fig. 31). Those in the superficial layers of the adventitia were mainly myelinated fibers; those in the deeper layers of the adventitia and the media were largely unmyelinated. Inasmuch as there is no reason to assume that somatic efferent fibers play a part in the

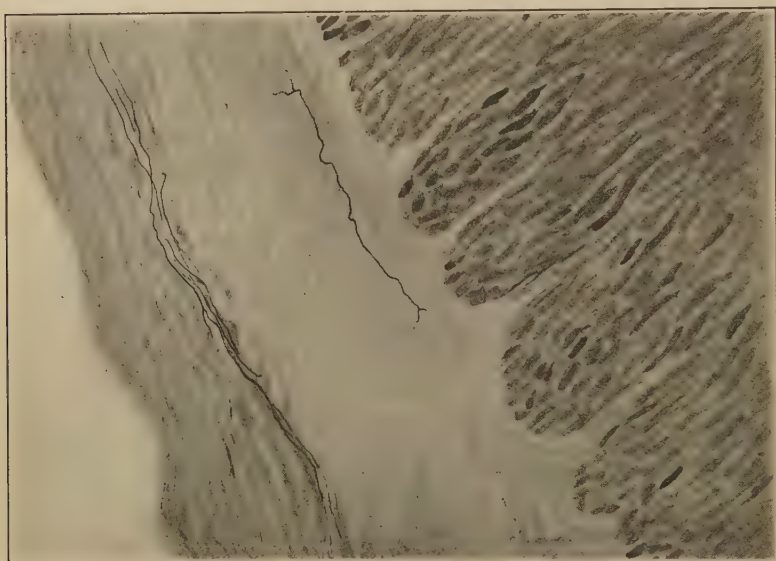


FIG. 31.—Drawing from a longitudinal section of the dorsalis pedis artery of a dog after degeneration of the sympathetic fibers, showing the presence of dorsal-root fibers in the adventitia. Nerve fibers indicated by black lines. (Kerper.)

innervation of blood vessels, the fibers which remain in the arterial walls following degeneration of the sympathetic supply must be regarded as dorsal root fibers. Whether any of these fibers are parasympathetic could not be determined by the experimental method employed.

After degeneration of the nerve fibers which were interrupted by section of the brachial and femoral arteries, the nerve supply was greatly reduced just distal to the section, but it was not appreciably altered in the distal portions of these arteries. On the other hand, preparations of the femoral artery of an animal which had been subjected to both section of the roots of the spinal nerves supplying

the hind limb and extirpation of the lumbar sympathetic trunk were entirely devoid of nerve fibers. These findings seem to warrant the conclusion that the arteries of the extremities receive their nerve supply mainly through branches of the nerves which lie in proximity to them, and that long fibers which extend distally along the brachial and femoral arteries play no important part in the innervation of the distal portions of these arteries and their branches. These findings are, in the main, corroborated by the results of Woollard's (1928) recent study, by the use of similar experimental methods, of the innervation of the arteries of the hind limb of the cat.

According to Woollard's findings in normal animals (rat, guinea-pig, cat, dog), bundles of nerve fibers extend from the plexus on the aorta along the iliac artery, forming an interlacing plexus. As these bundles are traced distally along the femoral artery, they gradually become smaller and disappear somewhere in the distal part of the femoral region. The femoral artery is joined by twigs from the adjacent nerves, the majority of which are very small. They are composed on the average of five to ten fibers. These twigs become more numerous as the arteries grow smaller. The arterioles, according to Woollard, "are enmeshed in the ramifications of the nerve bundles."

Distribution of Nerve Fibers in Vessel Walls.—Not a few of the older anatomists observed that nerves become intimately associated with the blood vessels and even penetrate the vessel walls. Knowledge of the finer structure of these nerves and their arrangement and distribution in the vessel walls awaited the development of specialized technique, particularly the intra vitam methylene blue and silver impregnation methods. It is now definitely known that, with few possible exceptions, all blood vessels, including arteries, veins and capillaries, are supplied by nerves.

The intrinsic nerves of arteries and veins are arranged in a more or less definite manner in the vessel wall. Certain investigators have described three more or less distinct plexuses in the walls of arteries. According to Michailow (1908), there is an outer plexus in the adventitia, a deeper plexus at the border between adventitia and media, and a deepest plexus in the media. He designated these plexuses respectively the "adventitial" plexus, the "border" plexus and the "muscular" plexus. Certain other investigators have not recognized a border plexus. They also question the advisability of regarding the nervous complex in the media as a plexus (Hirsch, 1926). That the adventitia and media are abundantly supplied with intrinsic nerve fibers is generally conceded. There is no general agreement at present regarding the existence of nerve fibers in the intima.

According to Hirsch (1926), who recently studied the distribution and arrangement of the nervous elements in the walls of the larger

vessels in the extremities in man, the nerve fibers in the adventitia do not constitute a plexus at any given depth in this layer, but nerve fibers occur in larger or smaller bundles throughout the entire adventitia. While, in general, the nerve fibers run longitudinally in the adventitia, there is no reason to assume that individual fiber bundles continue along the vessel for any considerable distance. The fibers are in part myelinated and in part unmyelinated. They enter the adventitia through slender rami arising from the somatic nerves. These rami can usually be traced but a short distance, if at all, along the vessel until they are lost in the adventitial tissue. The fibers of any one ramus do not all take the same course in the adventitia. The majority seem to run distally, but some run in the opposite direction. Not uncommonly the fiber bundles are arranged with reference to the vasa vasorum, but to what extent they are functionally related to these small vessels is not apparent from the histological picture. The vasa vasorum apparently afford convenient pathways for the nerve fiber bundles through the adventitial tissue. In most instances, a fiber bundle which joins one of these small vessels accompanies it for a short distance and then deviates from its course through the connective tissue and joins another of the vasa vasorum. Stöhr (1922) described the same relationship of the nerves in the adventitia to the vasa vasorum in the blood vessels of the pia mater and chorioid plexus. According to Hirsch, the capillaries in the adventitia are commonly accompanied by one or more nerve fibers, but it is quite impossible, on the basis of histological observations, to decide whether these fibers are functionally related to the capillaries or merely accompany them through the connective tissue.

Hirsch was not convinced, by the results of his studies, that the meshwork of nerve fibers in the adventitia should be regarded as a continuous plexus around the vessel, regardless of the abundance of its fibers. Other investigators (Michailow, 1908; Glaser, 1914; Woollard, 1928) have regarded it as a continuous plexus which completely encircles the vessel. According to Woollard, this plexus occupies all planes of the adventitia, and exhibits essentially the same arrangement in both the larger and smaller vessels.

The fiber complex in the media has also been described as a closed plexus encircling the vessel. Fiber bundles coursing through the adventitia enter the media. Some of them seem to be derived from the plexiform meshwork in the adventitia; others enter the media quite directly from the rami through which the fibers are conveyed from the somatic nerves to the vessel. These bundles contain relatively fewer myelinated fibers and a larger proportion of unmyelinated fibers of small caliber than those which ramify only in the adventitia (Kerper, 1927; Woollard, 1928). According to Michailow (1908), Dogiel (1910), and Glaser (1914), these nerves

constitute a plexus in the muscularis which, as described by Dogiel, is made up of numerous varicose unmyelinated fibers and spreads out over the surface of the muscle layer as well as between the muscle fibers throughout the media. Both Hirsch and Stöhr observed a plexus on the surface of the circular muscle, but failed to find nerve fibers in the deeper layers of the musculature. Kerper observed unmyelinated fibers of small caliber throughout the entire musculature. Woollard also found nerve fibers throughout the media. He described the intramuscular plexus as a real nerve net composed of fibers which divide, rejoin, and divide again, forming a continuous fibrous structure throughout the length of the vessels.

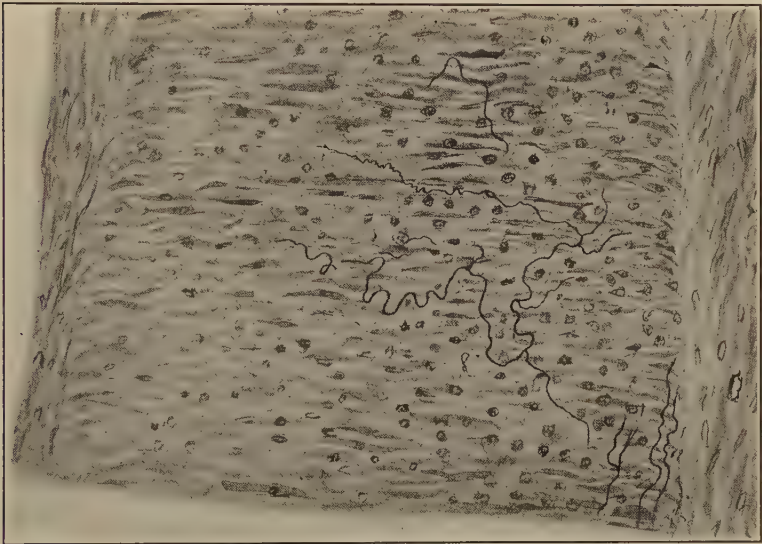


FIG. 32.—Drawing from a longitudinal section of the anterior tibial artery of a dog, showing anastomosis of nerve fibers in the media. (Kerper.)

Kerper's preparations also afford evidence of the existence of anastomosing fibers in the media (Fig. 32). In the aorta Woollard recognized a superficial and a deep plexus in the media.

Various authors have maintained that nerve fibers also occur in the intima. According to Glaser (1924), individual nerve fibers pass through the media and terminate in the intima. They are not abundant and do not form a plexus. He described them as frequently giving rise to branches which end in knob-like enlargements, some of which lie in close proximity to the endothelium. Among recent investigators, Hirsch, Stöhr and Kerper were unable to corroborate these findings.

The innervation of the veins has been studied less extensively

than that of the arteries. The meager data available, however, suggest that the general plan of distribution of the nerve components observed in the arteries also obtains in the veins, with such differences as may be correlated with the relative ratio of muscle to the other tissue elements in the vessels.

Do Ganglion Cells Exist in the Vessel Walls?—Not a few of the older investigators have maintained that ganglion cells occur either singly or aggregated in small ganglia in the walls of the larger arteries. No recent investigator has observed ganglion cells in the walls of any of the vessels of the extremities, but it is still maintained by some that ganglion cells occur in the walls of the aorta and the carotid and renal arteries. These cells are represented as being imbedded in the adventitial tissue. Glaser (1924) described and illustrated groups of ganglion cells in the aortic plexus and the plexus on the internal carotid artery, which he regarded as within the adventitial layer of the vessel wall. According to his account, these cells are essentially similar to the ganglion cells in the deep cardiac plexus. Ganglion cells have not been observed in the deeper layers of the wall of any blood vessel.

Ganglion cells are infrequently observed in close proximity to blood vessels in various parts of the body, particularly in the heart and bladder. These cells sometimes occur singly and sometimes in small ganglionic masses. They are usually not imbedded in the vessel wall. There is no reason to assume that they are functionally related to the vessel unless perchance they represent the peripheral components of visceral efferent chains which terminate in the vessel wall. Their proximity to the vessel probably is purely circumstantial.

Ganglion cells in the plexus on the internal carotid artery probably represent cells which were displaced from the superior cervical sympathetic ganglion during embryonic development, and do not differ essentially from the neurons in the latter ganglion. There is no reason to assume that such cells become functionally related to the internal carotid artery unless they constitute the terminal links in visceral efferent chains supplying this artery. The fact that such ganglia may become imbedded in the adventitial layer of the vessel wall does not necessarily indicate a functional relationship to the vessel.

Small ganglia probably are normal constituents of the aortic plexus. Like the major portion of this plexus, they usually lie superficial to the aortic wall. If any of them become imbedded in the adventitial layer of the aorta they probably are not, by reason of their more intimate relation to the aorta, differentiated functionally from the rest of the ganglia in the aortic plexus. The only known functional relationship of autonomic ganglion cells to blood vessels is that of peripheral neurons in visceral efferent chains.

Fiber Terminations and End Organs in Arteries and Veins.—

Fiber terminations and end organs of considerable variety have been described in the adventitia, particularly in the larger arteries and veins. The majority of these probably are receptive organs which represent the terminal structures of myelinated fibers. They fall roughly into two classes, viz.: (1) naked terminations consisting of terminal branches or terminal loops, and (2) encapsulated end organs. Each of these classes exhibits a wide range of variation. Naked terminations may consist of simple terminal branches which end in bulb-like enlargements, tree-like or brush-like endings, and very delicate loop-like structures which are sometimes relatively simple, and sometimes highly complex. The tree-like and brush-like endings occur very commonly in the adventitia of the vessels of the extremities (Hirsch, 1926). They also occur in the adventitia of the coronary arteries (Woollard, 1926). Encapsulated end organs in the adventitia are widely distributed and occur in considerable abundance. Hirsch stated that he observed as many as fourteen such bodies in a single section. They differ greatly in size and form, but exhibit the same general plan of architecture. In general, they are composed of layers of spindle-shaped cells which are separated from each other by interlamellar layers of non-cellular substance. In addition to the terminal loop of the nerve fiber, the interior of such a capsule contains a core of compact oval cells which, in silver preparations, usually appear darker than the surrounding tissue. Some of these end organs conform fully to the usual description of Pacinian corpuscles. Others resemble very closely the typical end bulbs of Krause. Still others exhibit a structure which may be regarded as intermediate between these two extremes. According to Hirsch, the encapsulated end organs occur only in the outer layers of the adventitia. Woollard (1928) emphasized the possible relationship to the blood vessels of certain encapsulated fiber terminations situated in the adjacent fatty tissue. In some instances, according to his findings, a medullated nerve fiber which terminates in the adventitia by means of one branch, also terminates in a sensory end organ lying in the fatty tissue adjacent to the vessel by means of another branch. Unencapsulated fiber terminations occur in all parts of the adventitia (Hirsch, 1926).

Nerve fiber terminations in the media have been described by relatively few investigators. These are mainly the terminations of unmyelinated fibers in relation to the smooth muscle cells. According to Glaser (1924), slender varicose fibers arising from the plexus in the media ramify among the muscle fibers and give rise to short branches. Some of these branches terminate on the muscle fibers in small bulb-like enlargements. Others, apparently, end in the musculature without terminal enlargements. Glaser's description of these terminal branches conforms closely to an earlier description

of them by Lapinsky (1905). The terminal structures apparently lie in contact with the muscle cells, and are not intracellular (Lapinsky, 1905; Woollard, 1928). In addition to the fiber terminations in direct relation to the muscle cells, Woollard (1928) described nerve fiber terminations in relation to certain large branching cells which exist in the media in both the larger and smaller vessels (Fig. 33). These cells are not regarded as nervous elements, but probably are related to the so-called Rouget cells. Woollard suggested that they may play a part in vascular reactions.

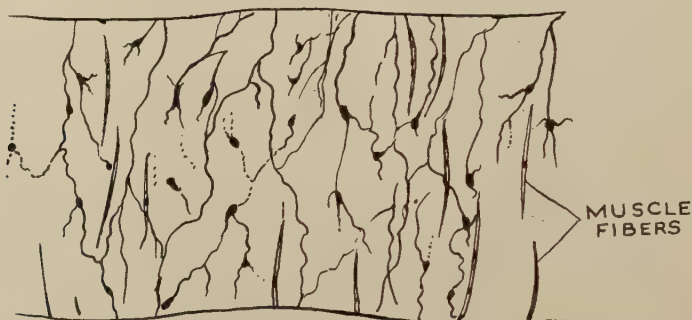


FIG. 33.—Large branching cells associated with the nerve plexus in the media in an artery of the cat. (Redrawn from Woollard: *Heart*, vol. 13; courtesy of Shaw & Sons, Ltd.)

Distribution of Nerve Fibers to Capillaries.—Capillary blood vessels are quite generally accompanied by unmyelinated nerve fibers which either run singly or in very small bundles. Such fibers have frequently been described and illustrated as running along the capillary, sometimes in close proximity with its wall, but more often separated from it by an appreciable interval. Actual points of contact or terminal structures in actual contact with a capillary which could be interpreted as structures through which the nerve fibers are functionally related to the capillaries have been observed and described by but few investigators. A functional innervation of capillaries has in recent years been quite generally conceded, partly by reason of observed anatomical relationships of nerve fibers to capillaries, but more especially by reason of the normal physiological behavior of the capillaries and their responses to sympathetic stimulation.

The innervation of the capillaries was recently investigated anew by Stöhr, Jr. (1926). In material taken from the human heart and bladder he was able to determine, by the use of Bielschowsky's method as modified by Gross, that unmyelinated fibers not only terminate on the capillary endothelium, but also frequently make contact with the endothelial cells through enlargements or flattened

expansions of the nerve fibers along their course. He advanced the opinion that the nerves are functionally related to the capillaries through specialized terminal structures and modified portions of the fibers which lie in contact with the capillary endothelium. He reiterated his earlier conviction, however, that the capillaries within the substance of the central nervous system are devoid of a nerve supply, although he had previously (1922) described terminations of unmyelinated nerve fibers on the endothelium of capillaries in the pia mater.

The nerve fibers accompanying the capillaries are derived in part from the nerve complex associated with the arterial branches from which the capillaries arise and in part from nerves which ramify in the adjacent tissue. The latter probably contribute the major portion of the nerve supply to the capillaries. Neither are all the fibers which accompany the capillaries functionally related to them. Many of these fibers, after following the course of capillaries for some distance, again deviate from them either for their terminal distribution, as in the case of many of the sympathetic fibers which supply skeletal muscle fibers, or to join another fiber bundle to be conveyed to a more peripheral destination, as in the case of many of the fibers distributed to the sweat glands and erector pili muscles. Neither do the fibers which reach the capillaries via the nerves in the adjacent tissues always mingle or interlace with other fibers accompanying the capillaries. Not infrequently individual fibers may be traced for appreciable distances along capillaries without any apparent relationship to other nerve fibers.

In general, the nerve fibers run along the capillaries but never lie in intimate contact with the capillary wall for any considerable distance. They usually run a somewhat tortuous course, coming in intimate contact with the capillary wall only at certain points. Again, a single fiber or a small bundle of fibers may turn away from the capillary and return to it again after a short course through the adjacent tissue. Stöhr, Jr., did not regard these relationships of nerve fibers to capillaries as fortuitous, but advanced the opinion that a functional relationship between a nerve fiber and a capillary may exist wherever the two are in actual contact with each other. This opinion is supported by the fact that not infrequently the smaller nerve fibers involved show an area of broadening and flattening in which the fibrils are more loosely aggregated than in other parts of the fiber at the points where they lie in contact with the capillary wall. Stöhr also emphasized the fact that the nerve fibers which are thus intimately related to the capillaries are all unmyelinated and of relatively small caliber.

The course of the nerve fibers associated with the capillaries, in general, conforms more or less closely to the course of the latter, at least for a short distance. Wherever the capillaries anastomose

freely, the accompanying nerve fibers are usually arranged in a loose-meshed plexus corresponding in a general way with the capillary plexus and interwoven with it. Individual capillaries are not always accompanied by nerve fibers throughout their entire length. Occasionally, it is impossible to find a nerve fiber in close proximity to a given capillary in the field of observation, but if the capillary can be followed for some distance in the preparation one or more nerve fibers may be observed to approach it from a neighboring capillary or a nearby fiber bundle and to continue along its course. The arrangement of the nerve fibers with reference to the capillaries is not simple, but relatively complex, varying somewhat with the complexity of the capillary plexus.

Although delicate terminal branches of nerve fibers which end on capillaries in bulb-like enlargements have been described by various investigators, including Krimke (1884), Natus (1910), and Ohno (1924), they have not been observed in large numbers. Furthermore, it is highly probable that the structures described as nerve terminations on capillaries were in some instances only artifacts. Stöhr, Jr., observed nerve terminations on capillaries but a few times. He concluded, on the basis of his findings, that direct contact of the nerve fibers with the capillary endothelium, especially at the points where the fiber is flattened and its fibrillar components are separated somewhat, plays a more important rôle in the functional relationship of the nerve fibers to the capillaries than specialized fiber terminations. He also observed that the nuclei of neurilemma cells which are associated with these delicate nerve fibers sometimes lie in intimate contact with the capillary endothelium, and suggested that, where this relationship obtains, functional contact of the nerve fiber with the capillary may be established through the nucleus of a neurilemma cell.

In view of the fact that the capillary wall contains no contractile tissue comparable with the musculature of the arteries and veins, the question arises as to whether the nerve fibers, which seem to be functionally related to the capillaries, are efferent or afferent in nature. As is well known, the Rouget cells, which are quite generally associated with the capillaries in the Amphibia, have been regarded as the contractile elements through which diminution in the caliber of the capillaries is brought about (Krogh, 1922). Similar cells have also been observed in association with capillaries in mammals. Rouget himself described such cells in the retina and fatty tissue in rabbits and certain ruminants. He also observed them in association with the capillaries in the brain in the latter animals. Vimtrup (1922) also found cells which he regarded as Rouget cells associated with the capillaries in the intestine of the mouse and in the interstitial and cutaneous connective tissue in man. The data available at present, however, do not warrant the

conclusion that Rouget cells are generally associated with the capillaries in mammals. Neither has it been demonstrated beyond question that they are the essential contractile elements through which capillary contraction is brought about even in the Amphibia. As observed by the Clarks (1925), capillary contraction may take place in the Amphibia quite independently of the Rouget cells. On the other hand, Bensley and Vimtrup (1928) observed actual contraction of the Rouget cells on the capillaries in the tongue of the living frog, and in the surviving nictitating membrane. Contraction of these cells, in the latter tissue, was elicited by repeated electrical stimulation. Bensley and Vimtrup were also able, by means of supravital staining with Janus green B, to demonstrate myofibrils in the Rouget cells which react to the stain in the same manner and at the same time as those in the muscle cells in the walls of the arterioles. These observations strongly suggest that the Rouget cells when present play a rôle in capillary contraction.

The nerve fibers which are most intimately associated with the capillaries resemble sympathetic fibers. They are, in the main, unmyelinated and finer than the fibers in the adventitia of arteries and veins which are generally regarded as afferent. Furthermore, at least a large percentage of the fibers which accompany the capillaries in skeletal muscles remains intact after degeneration of the fibers of spinal origin, following section of both dorsal and ventral nerve roots between the spinal ganglion and the communicating ramus (Kuntz, 1927). These observations strongly suggest that the nerve fibers associated with the capillaries are mainly fibers of sympathetic origin, which are essentially efferent in nature.

PHYSIOLOGY OF THE NERVES OF THE BLOOD VESSELS.

The functional control of the blood vessels depends in part on nervous influences and in part on the effects of hormones and other substances carried in the blood. The caliber of the blood vessels must play an important rôle in the functional state of the tissue or organ supplied by reason of its effect on the rate of the interchange of substances between the blood and the tissue elements. This rate varies both with changes in the volume of blood in the tissue and changes in the rate at which the blood flows. The volume of blood supplied to an organ in a given unit of time must vary directly with the caliber of the vessels. That, in general, the caliber of the vessels supplying an organ is increased, while the organ is physiologically active and diminished while it is at rest, is a fact of common observation. To what extent these changes depend on nervous influences and to what extent they represent the direct effect on the blood vessels of products of metabolism arising by reason of the

activity of the organ is not known. The vascular dilatation observed in active organs usually involves the capillaries to a greater extent than the arteries and veins. Since the capillaries are subject to nervous influences in a lesser degree than either the arteries or veins, the changes in caliber which they undergo under normal physiological conditions probably are quite independent of nervous influences. Direct responses of capillaries to nervous stimulation, however, cannot be denied.

The vasoconstrictor mechanism probably plays a dominant rôle in the nervous control of the blood vessels. Inasmuch as the vasoconstrictor fibers are conveyed to the blood vessels in the same nerves which also convey other fibers, the effect of impulses conveyed by these other fibers is not always apparent when the nerve trunk is stimulated. For example, stimulation of the fibers supplying a gland may inhibit secretion by reason of the constriction of its blood vessels elicited by stimulation of the vasoconstrictors, even though secretory impulses are reaching the gland cells. On the other hand, changes in the caliber of the blood vessels may follow stimulation of a nerve, though quite independently of vasomotor impulses. For example, stimulation of a nerve supplying skeletal muscle usually results in dilatation of the blood vessels in the muscle by reason of the effects of metabolic products arising as a result of muscular contraction. If, however, the muscle is curarized so that the motor terminations are paralyzed, stimulation of the nerve is followed by little or no dilatation of the blood vessels. Dilatation of blood vessels which follows nervous stimulation is in many cases only indirectly dependent on nervous impulses; consequently, it does not in such cases demonstrate the existence of vasodilator fibers. It cannot be denied, however, that certain vessels are supplied by both vasoconstrictor and vasodilator fibers.

Changes in the caliber of arteries and veins are brought about primarily through changes in the state of contraction of the musculature of these vessels, which consists of an inner circular and an outer longitudinal layer of muscle fibers. In most vessels the longitudinal muscle layer is but poorly developed. Vasoconstriction is brought about by the active contraction of the circular muscles which, in so far as it is neurogenic, depends on impulses conveyed through the sympathetic innervation of the vessels. Increase in the caliber of these vessels may be brought about by inhibition of the circular muscles, increased pressure sufficient to counteract the natural elasticity of the vessel walls, or active vasodilation. The *modus operandi* of the vasodilator fibers is not fully understood.

Although the capillaries have no actual musculature, they undergo changes in caliber which, at least in some instances, can hardly be accounted for as the result of changes in the caliber of arteries or

veins, with the capillaries playing only a passive rôle. As indicated above, the Rouget cells associated with the capillaries in certain animals have been regarded by some as the contractile elements through which capillary constriction is brought about. Krogh (1922) advanced the theory that each of these cells is supplied by a sympathetic fiber and that it contracts in response to nervous impulses conveyed by this fiber. Anatomical proof of the sympathetic innervation of the Rouget cells, however, is not forthcoming. Neither can the universal occurrence of Rouget cells associated with the capillaries be conceded. Richter and Natus (1910), who described changes in the caliber of capillaries in the rabbit's pancreas, found no Rouget cells associated with them. Neither could Ohno (1924) demonstrate their presence on all capillaries even in the frog. Stöhr, Jr. (1926) stated definitely that he never observed Rouget cells in mammals, including man, but he found abundant evidence of actual contact of nerve fibers with the capillary endothelium. Furthermore, as observed by the Clarks (1925), capillary constriction may occur in Amphibia quite independently of the Rouget cells.

Steinach and Kahn (1903), who first reported capillary contraction in response to sympathetic stimulation, observed it in the nictitating membrane of the frog. In their experiments electrical stimulation of the sympathetic trunk at the level of the second spinal nerve produced the same reaction of the vessels of the nictitating membrane as direct stimulation of the membrane itself. The capillaries contracted, but more tardily than the arterioles. Under favorable conditions the latent period for the capillaries amounted to four to five seconds. Krogh, Harrop and Rehberg (1922) also observed that when the lower part of the sympathetic trunk was stimulated electrically in the frog, the capillaries in the web of the foot contracted several seconds later than the arterioles. These results strongly suggest that the capillary constriction is secondary to the contraction of the arterioles. If it were the direct response of the capillaries to nervous impulses, we should expect capillary constriction to occur simultaneously with contraction of the arterioles, or at least without a long latent period. Again, following section of a sympathetic nerve, the arteries and arterioles affected dilate very promptly, but the capillaries only after a relatively long interval, usually one-half hour or longer. This also suggests that dilatation of the capillaries is not the direct result of denervation, but a passive process which is secondary to dilatation of the arterioles.

The results of recent investigations bearing on the causes of caliber changes in capillaries have lead to widely divergent conclusions. On the basis of independent studies, Jacobi (1920), Marschand (1923), Rehberg and Karrier (1923) and Nesterow (1925)

have supported the theory that changes in the caliber of the capillaries are, in general, secondary to changes in the caliber of the arteries, especially their terminal branches, including the arterioles. On the other hand, Pribram (1920), Merzt (1920), Nickau (1920-1921), Parrisius (1921), Kylin (1922), Jurgensen (1923), Hagen (1923), and Bensley and Vimtrup (1928) have supported the theory that the capillary walls contain contractile elements and that these vessels undergo changes in caliber in response to nervous influence. A third group of investigators, including Kukulka (1920), Moog and Ambrosius (1922), and Redisch (1923), have supported the theory that chemical stimuli constitute a major factor in the causation of caliber changes in the capillaries.

In an extensive study of the caliber changes in the capillaries in the nail folds in normal human subjects and in patients exhibiting auricular fibrillation, carried out by the aid of cinematographic records, Crawford (1926) found "no evidence that these changes are due to a peristaltic wave of contraction, a local rhythmic contractile action of the capillary, or a pulsatile motion conveyed to the blood stream and so to the capillary wall by the heart beat." He regarded the mechanism involved in the production of capillary caliber changes as unknown.

Krogh (1927) recently maintained that the capillaries, like the arteries, are influenced reflexly in many ways, and that the reflexes involved are carried out through sympathetic fibers. He was unable to produce caliber changes in peripheral capillaries by stimulation of the distal ends of dorsal spinal nerve roots, but regards localized hyperemia, due to stimulation of the skin, as the result of axon reflexes carried out through collaterals of the sensory fibers which mediate cutaneous pain. These axon reflexes, according to Krogh, bring about active dilatation of many of the capillaries in the cutaneous area involved.

The solution of the problems involved in caliber changes in capillaries is beset with inherent difficulties by reason of the marked hydrostatic effect on the capillaries of any changes in the caliber of the arterioles. It must be admitted that the data available at present do not afford an adequate explanation of caliber changes in capillaries.

The Vasomotor Nerves.—That the vasoconstrictor function is subserved through the sympathetic nerves is evidenced by the fact that all arteries and veins, with few possible exceptions, constrict in response to stimulation of their sympathetic nerve supply. The preganglionic neurons involved are components of the thoracic and upper lumbar nerves. Their distribution in the spinal cord is coincident with that of the thoracolumbar outflow to the sympathetic ganglia. Since, as pointed out above, nerve fibers extending from the plexuses on the aorta along the peripheral arteries play

no part in the innervation of the distal portions of these arteries, the vasoconstrictor fibers must be conveyed peripherally mainly through the somatic nerves, and reach the peripheral vessel through rami which join them at intervals throughout their entire extent.

Vasoconstriction in any considerable portion of the body brings about a rise in blood pressure throughout the entire system. For example, if the splanchnic nerves are stimulated, vasoconstriction is elicited throughout a large part of the splanchnic area; consequently, blood pressure rises and a greater volume of blood is forced toward the periphery. The peripheral blood vessels are dilated by reason of increased pressure. To what extent the increased output of adrenalin elicited by splanchnic stimulation plays a part in the increasing blood pressure under these conditions is not known. According to Gley and Quinquad (1921), splanchnic stimulation brings about an equal rise in blood pressure both before and after extirpation of the adrenal gland. Other authors have expressed the opinion that increased output of adrenalin plays a part in the rise in blood pressure following splanchnic stimulation. On the other hand, it is well known that changes in blood pressure are not determined by nervous influences alone. Still other vasoconstrictor substances in the blood, in addition to adrenalin, must be regarded as contributing factors.

When the vasoconstrictor fibers supplying a given area are severed the blood vessels in this area immediately dilate. This result probably is due to the removal of tonic impulses which normally flow out to the vessels in a more or less constant stream and maintain the musculature of the vessels in a state of tonus. After an interval which varies in different animals and at different times in the same animal, these vessels regain a degree of tonus and diminish in caliber. Not infrequently vessels deprived of their vasoconstrictor innervation in this manner become actually smaller in caliber than the normally innervated vessels of the opposite side, even before the possibility of regeneration of the vasoconstrictor fibers could be thought of. Since there are no ganglion cells along the walls of the peripheral arteries, it must be assumed that the musculature of the vessels develops a certain degree of tonus in the absence of nervous influences. This probably involves a reaction of the musculature of the vessels to vasoconstrictor substances in the blood. If only the preganglionic fibers are cut, leaving the sympathetic cells and fibers intact, the vessels regain tonus more promptly than if the postganglionic fibers are severed (Boshamer, 1925). This observation suggested to Schilf (1926) that the ganglionic neurons exert some influence on the musculature of the vessels even in the absence of preganglionic connections. On the other hand, the effect of adrenalin and perhaps other vasoconstrictor substances in the blood cannot be disregarded. It is conceivable

that these substances may influence the musculature of the vessels more readily in the presence of intact neuromuscular junctions than following degeneration of the postganglionic fibers.

It has been shown that stimulation of a peripheral nerve which contains both vasoconstrictor and vasodilator fibers, under certain conditions, elicits, not constriction, but dilatation of the vessels affected. If, for example, the sciatic nerve is cut, stimulation of its peripheral end commonly elicits vasoconstriction throughout the portion of the limb affected. If, after several days, the peripheral end of the sciatic is again stimulated, the observed result may be vasodilatation and not vasoconstriction. It is commonly assumed that this result is due to the fact that the vasoconstrictor fibers undergo degeneration more rapidly than the vasodilator fibers. These results not only suggest a method of investigation by which the distribution of vasodilator fibers can be determined, but also indicate an inherent difference in the vasoconstrictor and vasodilator fibers. The latter do not respond to stimulation in the same manner as the former and probably are not of sympathetic origin.

Rhythmic Activity of Blood Vessels.—Rhythmic contraction of blood vessels has frequently been observed following complete deprivation of nervous impulses. Following section of the cervical sympathetic trunk in the rabbit, rhythmic contractions are said to be absent in the vessels of the ears for several days only, after which they become reestablished. The continuation of rhythmic contractions in the vessels of the frog's foot following section of the sciatic nerve has also been observed. Furthermore, segments of arteries removed from the body may, under proper conditions, undergo rhythmic contraction (Meyer, 1913). Inasmuch as there are no ganglion cells in the vessel walls, the myogenic nature of rhythmic contraction of the vessels seems to be established. It does not follow, however, that even the rhythmic activities of the blood vessels are free from regulatory nervous influences. That the frequency of the rhythmic changes in the caliber of the vessels is independent of the pulse wave is indicated by the fact that their rate is normally much slower than the pulse-rate. In the vessels of the rabbit's ear, for example, it is usually once or twice per minute. The fact that rhythmic tonus changes may continue in isolated strips of arterial muscle also speaks against an influence of the pulse wave on the rate of the rhythmic caliber changes in the vessels. The functional significance of these rhythmic tonus changes in the vessels is not fully understood. According to certain investigators, they play no part in propelling the blood. On the other hand, Günther (1916) expressed the opinion that the work of the heart is augmented by them.

Reversed Action of Vasoconstrictor Fibers.—Under certain conditions, *e. g.*, following treatment of a vessel preparation with

ergotoxin, the normal effect of stimulation of the vasoconstrictor fibers may be reversed, *i. e.*, instead of constricting, the vessel may actually exhibit an increase in caliber (Dale, 1906). Pearce (1913) observed in perfusion preparations that adrenalin produced an effect similar to that of ergotoxin noted above, when the perfusion fluid contained no calcium. Schilf, Feldberg and Hahn (1926) also elicited dilatation of perfused vessels by sympathetic stimulation following the administration of appropriate doses of adrenalin. Bauer and Fröhlich (1918) advanced the theory that dilatation of the vessels, in these experiments, was elicited by stimulation of vasodilator fibers following paralysis of the vasoconstrictor fibers by the action of the drugs employed. If this theory could be verified, the existence of sympathetic vasodilator fibers would be established. As observed by Schilf and his co-workers, however, the effect of sympathetic stimulation is reversed by a definite dose of adrenalin. They pointed out that there is, at least for transfusion preparations of the frog, a threshold concentration of adrenalin beyond which sympathetic stimulation elicits vasodilatation, but until this threshold concentration is reached, sympathetic stimulation elicits vasoconstriction. They also observed that the blood vessels respond in a similar manner to varying concentrations of adrenalin in the absence of sympathetic stimulation, *i. e.*, until the threshold concentration is reached, adrenalin itself elicits vasoconstriction, and beyond this concentration, vasodilatation. When they repeated this experiment, following degeneration of the nerves supplying the vessels, the latter reacted to adrenalin in precisely the same manner. It appears, therefore, that the site of the drug action is somewhere beyond the nerve terminations. Consequently, they concluded that it is unnecessary to postulate two sets of nerve fibers, *viz.*: vasoconstrictors and vasodilators, in order to explain the observed reversed response of the vessels to sympathetic stimulation. In the presence of adrenalin the muscle cells apparently react to sympathetic stimulation according to their normal physiological mode until the threshold concentration of the drug is reached, but beyond this point they react according to a different mode of stimulation of the same set of fibers. The results of these experiments, therefore, do not prove the existence of sympathetic vasodilator fibers.

A discussion of the rôle of adrenalin in relation to the sympathetic innervation of the blood vessels is not within the scope of the present volume. These two factors are, however, intimately inter-related. Inasmuch as adrenalin does not act directly on the sympathetic ganglion cells or their axons, but, with few exceptions, exerts the same influence on smooth muscle cells as sympathetic stimulation, it may well be, as Elliott (1904) suggested, that these two means of stimulation were primarily parts of the same process,

and that the secretion of adrenalin is a necessary accompaniment of sympathetic impulses. With reference to the musculature of the blood vessels, this would imply that adrenalin is liberated with every sympathetic stimulation and acts directly on the muscle cells.

A notable exception to the similarity of the effect of adrenalin and sympathetic stimulation on blood vessels was pointed out by Carlson and Luckhardt (1921). They observed that in frogs and turtles the blood vessels in the lungs constricted in response to adrenalin, but no constriction of the vessels could be elicited by sympathetic stimulation. Stimulation of the vagi, however, did elicit constriction of these vessels. These results show clearly that the vessels in the lungs are innervated through the parasympathetic system in these animals, but they also react to adrenalin.

Central Vasoconstrictor Pathways and the Vasoconstrictor Center.—The preganglionic vasoconstrictor fibers, as stated above, emerge from the spinal cord in the thoracic and upper lumbar regions. Impulses conveyed by these fibers exert a constant tonic influence on the blood vessels. If the spinal cord is transected in the cervical region, the blood vessels at once lose tonus and become markedly dilated, particularly in the splanchnic and cutaneous areas. It may be inferred from this fact that the source of the tonic impulses is in the brain, and that fibers arising in a special group of cells descend in the brain stem and spinal cord and terminate in relation to cells in the intermediolateral cell column. Such a group of cells exists in the medulla and may be regarded as the vasoconstrictor center. The exact location of this center has not been determined histologically. The results of attempts to delimit it by physiological experimentation indicate that it lies in the tegmentum about the middle of the fourth ventricle and in the neighborhood of the superior olive and the nucleus of the facial nerve. Ranson and Billingsley (1916) also elicited marked changes in blood pressure in the cat by direct electrical stimulation in the floor of the inferior part of the fourth ventricle. Stimulation in the fovea inferior resulted in a marked rise in blood pressure, while stimulation in the area postrema, just lateral to the obex, resulted in a marked fall in blood pressure. They did not claim, however, that these points mark the location of special vasomotor centers, but suggested that they may be only the termini of afferent pressor and depressor fibers of the vagus nerves.

The cells in the vasoconstrictor center are stimulated reflexly by afferent impulses from various parts of the body. Vasoconstriction may be elicited by stimulation of the sensory portions of any spinal nerve and certain of the cranial nerves. On the basis of careful experimental studies, Ranson (1916) pointed out that the afferent impulses which initiate the pressor reflex are conducted by fibers which mediate protopathic sensation. They enter the spinal cord

through the lateral division of the dorsal nerve root and run into the fasciculus dorsolateralis at the apex of the posterior horn. The peripheral fibers run but a short distance in the fasciculus dorsolateralis, and probably terminate in the substantia gelatinosa Rolandi. The pressor impulses are probably conveyed upward in the cord through a series of short fibers which take origin in the substantia gelatinosa and run in the fasciculus dorsolateralis. They are conveyed up the spinal cord on both sides but somewhat better homolaterally. The corresponding efferent spinal vasomotor pathways are located either in the anterior or lateral funiculi. They are not interrupted by section of the posterior funiculi and the posterior horns. There is some evidence which indicates that a small percentage of the vasoconstrictor reflexes are carried out through centers in the spinal cord (Ranson and Billingsley, 1916).

By reason of the differential effect of reflex vasoconstrictor stimulation, it must be assumed that the cells in different parts of the vasoconstrictor center are connected, by definite aggregates of fibers, with the vasoconstrictor neurons which supply various regions of the body. For example, some of the cells control the activities of the vessels of the skin, and others those of the vessels of the splanchnic area. It must also be assumed that, under physiological conditions, the cells in different parts of the center may be acted upon separately.

Vasodilator Nerves.—The existence of special sympathetic vasodilator fibers has not been demonstrated. The dilatation of the blood vessels which sometimes follows stimulation of a mixed nerve containing both sympathetic and somatic fibers can be explained either as the result of antidromic conduction in dorsal root fibers or as the effect of metabolic products resulting from the activity of the muscle or gland cells stimulated. In like manner the vasodilatation which, under certain conditions, follows the stimulation of unmixed sympathetic nerves can also be explained without postulating special sympathetic vasodilator fibers. Certain of the older investigators reported findings which seemed to indicate the occurrence of special vasodilator fibers in the cervical sympathetic trunk. They claimed to have observed, not constriction, but dilatation of the vessels in the rabbit's ear following stimulation of the peripheral end of the cervical sympathetic trunk several days after the trunk had been cut between the superior and middle cervical ganglia. This result seemed to indicate the presence of vasodilator fibers in the cervical sympathetic trunk, which undergo degeneration less rapidly than the vasoconstrictor fibers.

Feldberg and Schilf (1926) could, under no conditions, elicit vasodilatation in the rabbit's ear by stimulation of the cervical sympathetic trunk. Following section of the cervical sympathetic trunk, stimulation of its peripheral end, in their experiments, always

resulted in constriction of the vessels until degeneration had advanced so far that stimulation was no longer effective. This state was reached on the fourth day following operation. These results are in accord with the earlier findings of Vulpain (1878) and Dastre and Morat (1892). It is probably safe to conclude, on the basis of findings of this nature and other physiological data to be considered below, that the thoracolumbar preganglionic components do not include special vasodilator fibers.

That stimulation of the cervical sympathetic trunk results in flushing of the mucosa of the mouth and pharynx is well known. This vasodilatation probably is only an indirect result of sympathetic stimulation and represents the reaction of the blood vessels to the products of secretion of the glands so abundant in that region, which were thrown into action by the sympathetic stimulation. Dale (1906) showed very clearly that vasodilatation which is entirely independent of direct nervous influences commonly accompanies glandular activity. In the case of the submaxillary gland he also showed that, following administration of ergotoxin which paralyzes the sympathetic fibers, stimulation of the sympathetic trunk elicits neither glandular activity nor vasodilatation. If special vasodilator fibers were present in the cervical sympathetic trunk, vasodilatation should be elicited under these conditions, since inhibitory fibers are not paralyzed by ergotoxin.

Weak electrical stimulation of the splanchnic nerves also results in dilatation of the affected vessels. Cannon and Lyman (1913) showed, however, that splanchnic stimulation does not elicit vasodilatation following extirpation of the adrenals. Since adrenalin in minute quantities causes vasodilatation, it may be assumed that the vasodilatation following weak splanchnic stimulation is the result of the minute quantities of adrenalin liberated. Conclusive proof of the existence of special vasodilator fibers in the splanchnic nerves is not forthcoming.

That the parasympathetic nerves contain vasodilator fibers is well known, but a general distribution of vasodilator fibers throughout the parasympathetic system is not universally conceded. Vasodilatation brought about by parasympathetic stimulation can, in many instances, be explained without assuming the presence of vasodilator fibers. For example, the vasodilatation which accompanies glandular activity in response to stimulation of the chorda tympani can readily be explained as the result of secretory activity. Salivary secretion is generally accompanied by some degree of vasodilatation; but if the salivary ducts are ligated glandular activity is retarded and the vasodilatation is diminished (Bancroft, 1906-1907). Furthermore, when the secretory activity of the submaxillary gland is held in abeyance by the effect of atropin, stimulation of the chorda tympani does not elicit vasodilatation, although

atropin does not paralyze vasodilator fibers. On the other hand, Anrep and Evans (1920) have shown that stimulation of the chorda tympani elicits vasodilatation in the tongue. This result strongly suggests the existence of vasodilator fibers in the chorda tympani and efferent rami arising from the submaxillary ganglion.

Not a little physiological evidence also indicates the existence of preganglionic vasodilator fibers in the glossopharyngeal nerve, which supply blood vessels in the region of the parotid gland, tonsils, pharynx and posterior third of the tongue. The sacral parasympathetic nerves also contain vasodilator fibers.

That the dorsal roots of certain of the spinal nerves convey fibers which conduct vasodilator impulses was maintained by Stricker as early as 1876. He observed dilatation of the blood vessels and a rise of temperature in the dog's foot in response to stimulation of the distal ends of the divided dorsal roots of the sixth and seventh lumbar nerves. This observation was corroborated by Gärtner (1889), Morat (1892), Worziloff (1896) and other more recent investigators. Bayliss (1901) obtained marked dilatation of the blood vessels of the hind limb by stimulation of the dorsal roots of the fifth, sixth and seventh lumbar and first sacral nerves. He maintained that the vasodilator fibers in the dorsal roots of these nerves do not traverse the sympathetic trunk, but extend directly into the lumbosacral plexus. In view of the fact that he failed to observe degeneration following section of the dorsal nerve roots proximal to the spinal ganglia, but did observe it following removal of the spinal ganglia, he advanced the opinion that the vasodilator fibers in the dorsal nerve roots in question are not true efferent nerve components, but are identical with sensory components, and subserve vasodilatation by virtue of their capacity for antidromic conduction. On the basis of further experimental results, he concluded that the vasodilator fibers of the fore limb of the dog are components of the dorsal roots of the sixth, seventh and eighth cervical and first thoracic nerves. Langley (1901) also interpreted vasodilatation in the hind limb in response to stimulation of the dorsal roots of the lower lumbar nerves, on the basis of antidromic conduction.

Bayliss concluded, on the basis of an intensive study of the reaction of the blood vessels to stimulation of dorsal root fibers, that this reaction involves a relatively long latent period (two to eight seconds in the dog) and exhibits a long after-effect. According to his observations, vasodilatation may persist ten minutes or longer after the stimulus has been removed. This seems to be characteristic of antidromic stimulation. Furthermore, the effects of antidromic conduction have been observed only on blood vessels and always involve vasodilatation.

Langley (1923) pointed out, on the basis of studies carried out

on cats and dogs, that the distribution of the antidromic fibers through a peripheral nerve, in general, coincides with its sensory distribution. Having determined the exact distribution of certain cutaneous nerves, he studied the effect of stimulation of the dorsal nerve roots following section of certain cutaneous branches. For example, after section of the superficial ramus of the median plantar nerve in the cat, stimulation of the dorsal root of the seventh lumbar nerve, from which the fibers of the median plantar nerve are derived, no longer elicited vasodilatation in the corresponding cutaneous area. This result seems to support the theory advanced by Bayliss, that the antidromic fibers which mediate vasodilator impulses, like the sensory fibers, arise from spinal ganglion cells.

If the antidromic fibers which, under experimental conditions, convey vasodilator impulses were physiologically antagonistic to the vasoconstrictor fibers, we should expect that, following section of the dorsal root fibers, leaving the ventral roots and communicating rami intact, the blood vessels involved would exhibit diminution in caliber by reason of the absence of the inhibitory impulses conveyed by the antidromic fibers. This, however, has not been observed. Section of the dorsal root fibers apparently does not affect the tonus or caliber of the blood vessels after the effect of the primary stimulation caused by section of the fibers has subsided. It is, therefore, not apparent that antidromic conduction plays any part in the maintenance of the normal tonus of blood vessels. Neither is there conclusive evidence that it is a normal physiological process. It may be but an artificial product of physiological experimentation. As pointed out above, the reactions of the vessels to antidromic stimulation differ from their reactions to sympathetic stimulation, in that they manifest a longer latent period as well as a delayed after-effect. Furthermore, second and third stimulations of the antidromic fibers are usually less effective than the first. These facts indicate that the muscle cells react to antidromic stimulation according to a different mode than to sympathetic stimulation.

Langley advanced the theory that antidromic impulses affect especially the smaller arteries and capillaries. He did not believe that they affect the arterial musculature directly, but maintained that either the afferent fibers sustain some peculiar relationship to the capillaries, or vasodilatation following stimulation of the antidromic fibers, is an indirect result of nervous influences. Bayliss expressed the opinion that afferent fibers bifurcate near the periphery and that one branch terminates in sensory end organs in the skin or muscle, while the other terminates in the musculature of an arteriole. Neither of these views has found anatomical verification. Nor does the conception of a terminal division of nerve fibers into branches which differ functionally harmonize with current physiological

conceptions of the neuron. Data are not wanting, however, which seem to indicate quite clearly that impulses received at the periphery may be conveyed centralward to the location of the assumed bifurcation and from that point via the vascular branch to a blood vessel where it elicits vasodilatation. As is well known, stimulation at the periphery may elicit local vasodilatation even after section of the afferent fibers proximal to the location of the assumed bifurcation. It seems not improbable that local erythema may involve a peripheral mechanism of this kind.

That impulses conducted outward through the dorsal roots of certain of the spinal nerves may elicit vasodilatation is now quite generally admitted by physiologists. In spite of the evidence in support of the theory of the antidromic conduction of these impulses, however, the identity of the vasodilator fibers with sensory fibers is not generally admitted. The opinion that vasodilator fibers which emerge through dorsalspinal nerve roots arise from nerve cells in the gray matter in the spinal cord has been advanced repeatedly, but anatomical proof of the existence of efferent fibers in the dorsal nerve roots was not forthcoming. As stated above, Ken Kuré *et al.* (1928) have recently advanced certain experimental anatomical data which seem to indicate the existence, in the dorsal roots of the sixth and seventh lumbar nerves in the dog, of efferent fibers which arise from nerve cells located in the basal portion of the dorsal horn in the spinal cord. They also advanced the opinion that these fibers effect synaptic connections in the spinal ganglia with special nerve cells which send their processes peripherally in the spinal nerves. If these findings are confirmed they will constitute an important contribution to our knowledge of the anatomical and physiological relationships of the vasodilator fibers distributed to peripheral blood vessels.

The Depressor Reflex.—Although the data available at present afford no conclusive evidence of a general distribution of vasodilator fibers either of sympathetic or parasympathetic origin, the existence of a vasodilator reflex mechanism cannot be denied. According to the current teaching, stimulation of the depressor nerve invariably results in a fall in blood pressure. Hunt (1895) also showed, under carefully controlled conditions, that depressor reflexes may be elicited by stimulation of most any afferent nerve. Not uncommonly, when a nerve is chilled, the same stimulus which before elicited a rise, elicits a fall in blood pressure. Very weak stimulation of any afferent nerve, except perhaps the splanchnic, almost invariably elicits depressor reflexes, while strong stimulation of any afferent nerve, except the so-called depressor nerve, elicits pressor reflexes. These facts have given rise to the assumption that two kinds of afferent vasomotor fibers exist, which have been called pressor and depressor nerve fibers respectively.

Ranson and Billingsley (1916) presented experimental data which indicate that the afferent depressor impulses, like the afferent pressor impulses, are mediated by the peripheral fibers which also mediate protopathic sensations. Whereas the pressor impulses are conveyed upward in the spinal cord at the apices of the posterior horns through paths composed of short fibers with frequent relays, the depressor impulses, according to their findings, are conveyed upward in the ventral parts of the lateral funiculi through paths composed of long fibers with few relays. Consequently, the resistance of the depressor paths is low as compared to that of the pressor paths.

The differences in the vasomotor responses elicited by weak and strong stimulation of afferent nerves, according to Ranson and Billingsley, can readily be explained by the difference in the resistance to afferent conduction offered by these two central pathways. Weak impulses reaching the spinal cord are conveyed upward in the depressor path and result in vasodilatation, with a fall in blood pressure. Whether they also inhibit the tonic action of the vasoconstrictor center is not clear. Within a certain range of stimulation, constriction and dilatation balance each other with little change in pressure. Vasodilatation probably is masked rather than inhibited. As stimulation becomes stronger, impulses ascend in the pressor paths in sufficient volume to bring about vasoconstriction and a consequent rise in blood pressure. It is quite unnecessary to assume inhibition of a vasodilator center in any case. The action of the vasoconstrictor fibers is more powerful than that of the vasodilators. Furthermore, the former are more widely distributed than the latter; consequently, strong stimulation normally results in a rise in blood pressure.

Depressor reflexes are elicited more readily through the vagus and glossopharyngeal nerves than through the spinal nerves. According to the current teaching, stimulation of the depressor branch of the vagus elicits only depressor reflexes. Accordingly, it has been assumed that the depressor nerve is composed exclusively of afferent depressor fibers. It has also been assumed that the vagus and glossopharyngeal nerves contain relatively more depressor fibers than the spinal nerves. This assumption probably is unwarranted, since the vagus and glossopharyngeal are visceral nerves whose afferent fibers terminate directly in the visceral afferent column in the medulla. Stimulation of the trigeminal nerve elicits vasomotor reactions comparable to those elicited by stimulation of the spinal nerves. This nerve contains somatic afferent fibers whose central connections are comparable with those of the somatic afferent fibers of the spinal nerves. Consequently, its pressor and depressor reactions can be explained on the same basis,

Is There a Vasodilator Center?—The existence of a depressor reflex mechanism, including known ascending conduction paths in the spinal cord, implies the existence of a center for vasodilator reflexes. Whether this center is anatomically distinct or incorporated in the general vasomotor center is not known. Ranson and Billingsley (1916) have shown that direct faradic stimulation of a point in the floor of the fourth ventricle within the area postrema, just lateral to the obex, results in a fall in blood pressure. They did not maintain that this point represents the location of the vasodilator center, although it seems not improbable that such is the case. Not all vasodilator reflexes, however, involve a center in the brain. If, in the dog, the spinal cord is severed in the lower thoracic region, reflex erection of the penis may still be elicited by stimulation of the glans. This fact indicates a reflex center in the lumbar region of the spinal cord for the vasodilator fibers supplying the penis. The data available at present do not indicate a single delimited group of nerve cells in any part of the nervous system with which all vasodilator fibers are functionally connected.

CHAPTER VIII.

INNERVATION OF THE RESPIRATORY SYSTEM

EXTRINSIC NERVES OF THE RESPIRATORY TRACT.

THE respiratory tract, including the larynx, trachea, bronchi and lungs, is innervated through the vagus and sympathetic nerves. The vagus innervation of the larynx and trachea is supplied mainly through the laryngeal branches of the vagi. Their sympathetic supply is derived mainly from the superior cervical sympathetic ganglia through the pharyngeal plexus and the sympathetic rami which join the vagi. The bronchi and lungs are supplied mainly through the pulmonary plexuses which are made up of vagus and sympathetic components plus the neurons in the pulmonary ganglia.

The superior laryngeal nerve is a branch of the vagus which receives its motor fibers from the accessory nerve. It passes downward and medially toward the thyroid cartilage and ends by dividing into a large internal and a small external laryngeal branch. It is joined by rami from the pharyngeal plexus and the sympathetic. The external laryngeal branch supplies the mucous membrane of the larynx, reaching upward to the epiglottis and the base of the tongue. It communicates inferiorly, beneath the lamina of the thyroid cartilage, with the inferior laryngeal nerve, and also supplies motor fibers to the cricothyroid muscle. All the other muscles of the larynx derive their motor nerve supply from the inferior laryngeal nerve, which is a terminal branch of the recurrent nerve. The latter nerve also supplies branches to the trachea, and is not uncommonly joined by a ramus from the middle cervical sympathetic ganglion. According to Tscheliustkin's (1927) findings in the dog, the nerves which approach the trachea and bronchi give rise to a loose-meshed plexus in the connective tissue along the ventral and lateral aspects, and another along the dorsal aspect of these organs. Minute ganglia occur sparsely scattered in the former plexus. The latter contains a large number of ganglia of various sizes and forms. These plexuses are continuous distally with the pulmonary plexuses.

As the vagus nerve on each side reaches the dorsal aspect of the root of the lung in man, it breaks up into numerous branches which become incorporated in the posterior pulmonary plexus. Some fibers from each vagus nerve pass over the upper border of the root of the lung and enter the much smaller anterior pulmonary plexus.

These plexuses are intimately connected with each other and with the cardiac plexuses.

The anterior pulmonary plexus lies in contact with the root of the lung anteriorly. It is joined on both sides by a few fibers from the corresponding part of the deep cardiac plexus, and on the left side also by fibers from the superficial cardiac plexus. It supplies structures in the anterior part of the root of the lung.

The posterior pulmonary plexus lies behind the root of the lung. It is made up mainly of branches of the vagus and slender rami from the second, third and fourth thoracic sympathetic ganglia. This plexus gives rise to numerous branches which form delicate plexuses on the bronchi and vessels as they enter the substance of the lung.

INTRINSIC NERVES OF THE RESPIRATORY TRACT.

The respiratory tract contains an abundant intrinsic nerve supply, including large and small myelinated and unmyelinated fibers and numerous ganglia, some of which contain but few and others a relatively large number of neurons. In general, these neurons are similar to those in the cardiac and enteric plexuses. They are to be regarded as parasympathetic and constitute the ganglionic components of vagus efferent chains. Ganglia occur in the walls of the larynx, epiglottis, trachea and larger bronchi, but are most numerous in the posterior wall of the trachea (Polschko, 1897). No ganglion cells have been found beyond the larger bronchi (Larsell, 1921). In general, the larger fiber bundles in the walls of the respiratory passages run longitudinally, but branch and anastomose freely to form plexuses. In the larynx there is a subepithelial and a deep plexus, the latter alone containing ganglia. In the epiglottis Polschko recognized only a subepithelial plexus. Both the subepithelial and deep plexuses are present in the walls of the trachea and larger bronchi. In the walls of the smaller bronchi the two plexuses blend into one. This plexus can be traced as far as the respiratory bronchioles, but nerve fibers running either singly or in small bundles continue still farther into the walls of the alveoli (Larsell, 1921). In the lungs of a human fetus, 15 cm. in length, Retzius (1893) described the terminal branches of nerve fibers in the necks of the alveoli. He also reported the occurrence of occasional nerve fibers in the alveolar walls.

The bronchial plexuses are continuous with the tracheal plexuses, but are made up mainly of fibers derived from the anterior and posterior pulmonary plexuses. According to Larsell (1922), the nerves which enter the lungs from the latter plexuses are distributed to the bronchi, blood vessels and visceral pleura. Perhaps the majority of fibers enter the bronchial plexuses. The subepithelial plexus is located mainly between the cartilaginous plates and the

bronchial musculature; the deep plexus is located between the cartilaginous plates and the parenchyma of the lung. The intrapulmonary ganglia are located chiefly in the latter plexus. They usually occur at the bifurcations of the bronchi and at the points of junction of the larger fiber bundles in the plexus.

The plexuses in the walls of the respiratory passages include both myelinated and unmyelinated fibers. Many of the larger myelinated fibers can be traced to terminations of a sensory type in the epithelium and subepithelial tissue as far distally as the bronchioles and atria. Doubtless, these are general visceral afferent fibers mainly of vagus origin. Other myelinated fibers terminate in the intrinsic ganglia in pericellular networks. Doubtless, these are preganglionic fibers of vagus origin. Following unilateral vagotomy in the rabbit, Larsell and Mason (1921) found that nearly all the pericellular networks in the intrapulmonary ganglia of the homolateral side underwent degeneration. They concluded that the few which remained intact represent the terminations of preganglionic vagus fibers from the contralateral side. There is no evidence that preganglionic fibers of spinal origin terminate in the ganglia in the walls of the respiratory tract. The smallest myelinated and the unmyelinated fibers are mainly fibers of sympathetic origin and axons of the neurons in the intrinsic ganglia. They are the postganglionic fibers which supply mainly the musculature of the respiratory tract. The mucous glands in the walls of the respiratory tract also receive postganglionic fibers mainly from the subepithelial plexus.

NERVE TERMINATIONS IN THE RESPIRATORY TRACT.

Sensory Terminations.—Polschko (1897), using the methylene-blue technique, described three types of sensory fiber terminations in the larynx and epiglottis, viz.: end arborizations and end bulbs or knobs, located in the subepithelial tissue, and branched endings which ramify in the epithelium. These terminal structures are connected with relatively large myelinated fibers which may be regarded as fibers of cerebrospinal origin. He also described the terminations of unmyelinated fibers, which he regarded as postganglionic, in the musculature of the larynx and trachea.

The nerve terminations in the lung of the rabbit were described in detail by Larsell (1921). Using the methylene-blue technique, he found sensory nerve endings in the epithelium of the primary bronchi at the points of origin of the bronchi of the various orders and in the walls of the atria. The sensory nerve terminations in the epithelium of the primary bronchi are highly complex. Relatively large myelinated fibers deviate from the fiber bundles in the plexiform meshworks around the bronchi and approach the bronchial

epithelium either singly or in bundles of two or three fibers. Individual fibers penetrate the epithelium and terminate in elaborate ramifications among the epithelial cells. These ramifications show



FIG. 34.—*A*, Sensory nerve termination in the epithelium of a primary bronchus within the lung in the rabbit. *B*, Sensory nerve termination at the point of division of one of the larger bronchi in the rabbit. (Larsell.)

numerous varicosities and each terminal branch ends in a slight enlargement. Some of the terminal branches approach the surface of the epithelium, but most of them lie relatively deep between the

columnar cells (Fig. 34). The ramifications of the larger terminations occupy an area approximately 150 microns in length and 125 microns in width. Similar terminations in the epithelium of the larger bronchi were described by Berkeley (1893) in Golgi preparations.

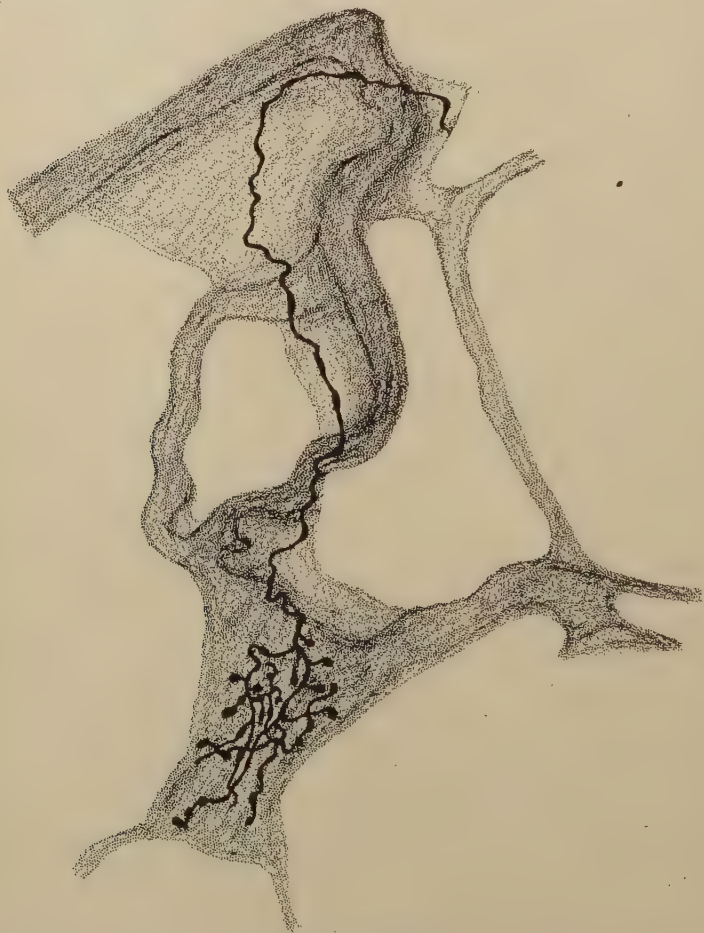


FIG. 35.—Sensory nerve termination at the division point of a small bronchus in the rabbit. (Larsell.)

The sensory nerve terminations in the epithelium of the successively smaller bronchi are essentially similar to those in the epithelium of the primary bronchi, but less elaborate and smaller. The most characteristic position of these terminations is in the angle between two bronchi of successive orders, where not uncommonly masses of lymphoid tissue lie in close proximity to the epithelium in which the nerve termination is located (Fig. 35).

The sensory nerve terminations situated at the points of division of the bronchioles and alveolar ducts differ somewhat from those in the larger bronchi. They are not only smaller, but their terminal branches are curved and appear somewhat drawn together, in contrast with the extended and radiating terminal branches of those located in the larger bronchi. The most distal sensory nerve

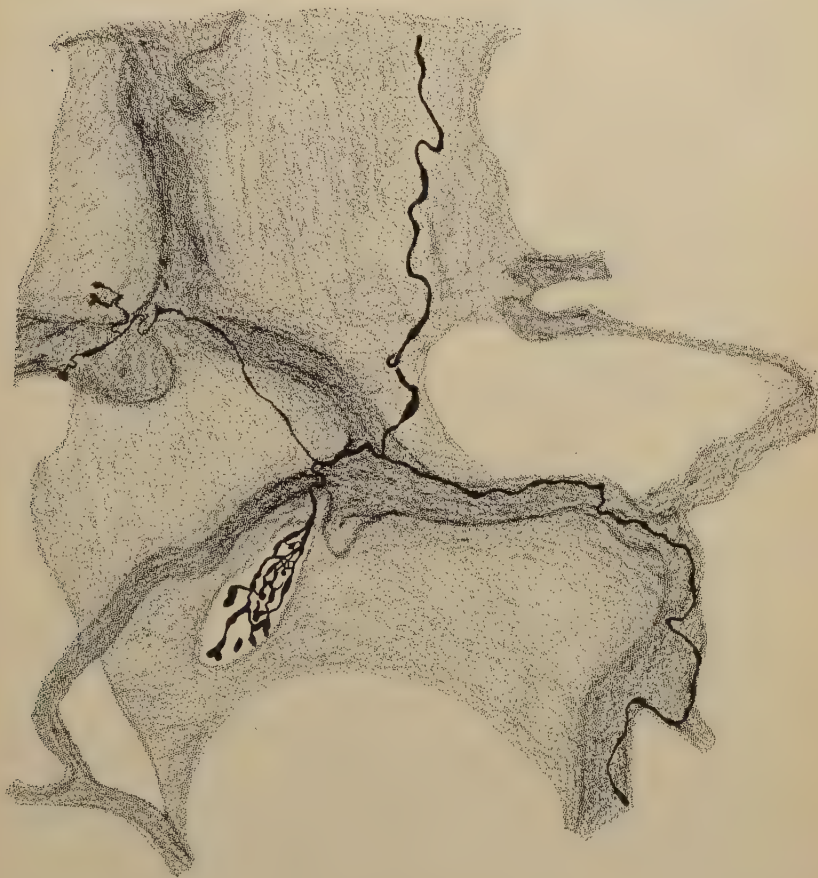


FIG. 36.—Sensory nerve terminations in the wall of an atrium in the rabbit. (Larsell.)

terminations described by Larsell are located in the epithelium just inside the atria at their connections with the alveolar ducts. These are small terminations lying in the wall of the atrium, just beneath the squamous epithelium which in part forms the delicate capsule by which they are enclosed (Fig. 36).

Motor Terminations.—The musculature of the larynx, trachea, and bronchi is richly supplied by nerve fibers which are easily

distinguished from the majority of the sensory fibers described above by reason of their smaller caliber and the fact that they are either unmyelinated or invested with a very thin myelin sheath. Many of these fibers can be traced directly from neurons in the

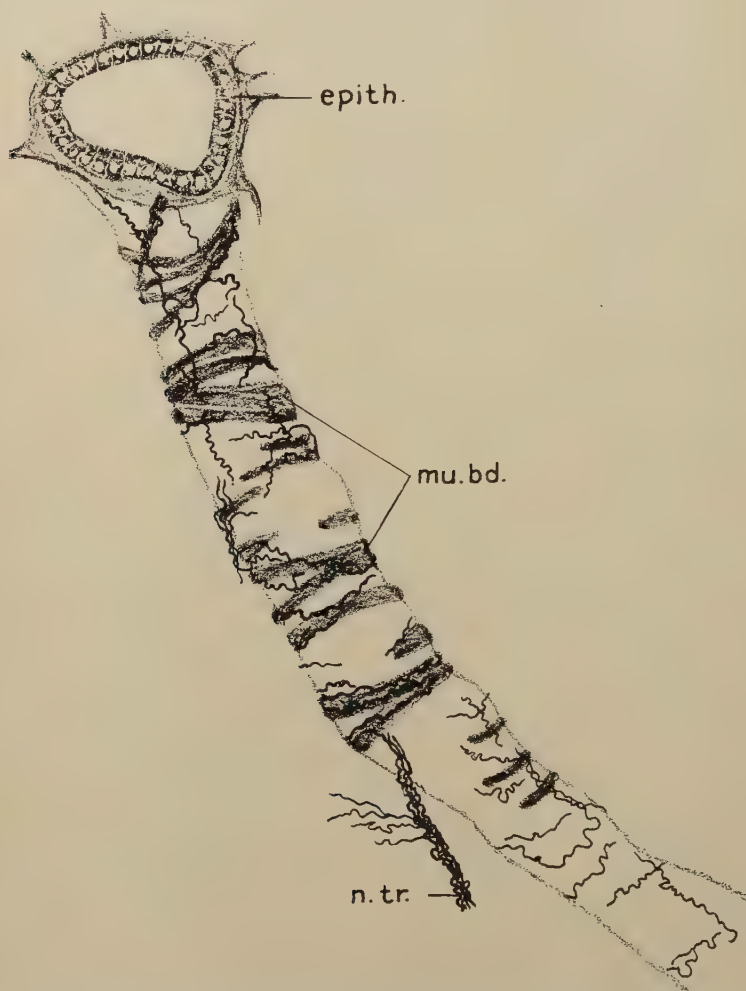


FIG. 37.—Nerve terminations on the muscle bands of a bronchiole in the rabbit.
(Larsell.)

intrinsic ganglia; others merely traverse these ganglia on the way to their peripheral distribution. The latter are postganglionic fibers which have their origin in ganglia of the sympathetic trunk.

In the larger bronchi the bundles of nerve fibers in general run

parallel to the smooth muscle bands. At intervals, nerve fibers deviate from these bundles, either singly or in small strands, and penetrate the muscle. On reaching the muscle the individual nerve fibers give rise to numerous slender branches which run between the muscle fibers and at intervals give off short twigs which terminate near the nuclei of the smooth muscle cells. Nerve bundles, constantly diminishing in size, may be traced as far as the bronchioles and alveolar ducts. From these bundles fibers may be traced into the musculature of the bronchioles and the sphincter-like bands at the openings of the alveolar ducts into the atria. No muscle fibers occur distal to these bands (Miller, 1921).

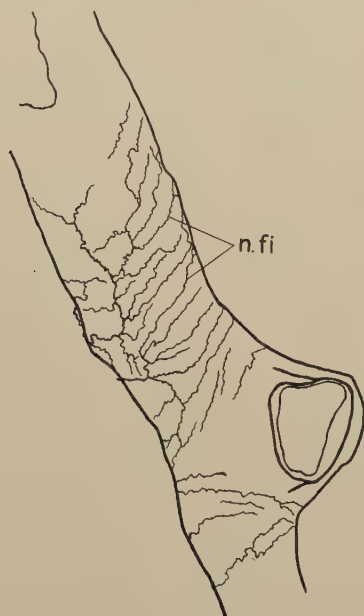


FIG. 38.—Distribution of nerve fibers in the musculature of the pulmonary artery in the rabbit. (Larsell.)

INNERVATION OF THE PULMONARY VESSELS.

The pulmonary artery and its branches are more richly supplied with nerves than the usual anatomical descriptions and the results of physiological experimentation seem to indicate, but less richly than the bronchial arteries. In the rabbit, according to Larsell (1921), relatively large nerve trunks become associated, near the hilum of the lung, with the larger branches of the pulmonary artery. These nerves wind about the blood vessels as they continue distally and, at irregular intervals, give off fibers which run roughly parallel

to the artery for a short distance, and then turn almost at right angles and divide into several main branches, one of which usually runs proximally and another distally along the artery (Fig. 38). These branches in turn give rise to smaller varicose branches, which may undergo still further subdivision and finally penetrate the media to terminate in relation to the smooth muscle cells. Karsner (1911) described a similar arrangement of nerve fibers in the walls of the pulmonary arteries in the dog. Larsell also observed sensory nerve terminations in the adventitia of the pulmonary arteries in the rabbit. These terminations are connected with relatively large myelinated fibers like those which may be traced to the sensory terminations in the bronchi.

The pulmonary veins have a relatively meager nerve supply, but the nerve fibers observed in relation to the media bear the same relation to the musculature as in the pulmonary arteries (Berkeley, 1893; Larsell, 1921). The pulmonary capillaries are also supplied by nerve fibers which form a delicate plexus in relation to the capillary wall. Larsell was able, in some of his preparations, to observe such nerve plexuses on the capillaries in the walls of the atria and air sacs.

The efferent nerve supply of blood vessels is mainly sympathetic, but it is highly probable that the vagus also contributes to the innervation of the pulmonary vessels. Both Berkeley (1893) and Larsell (1921) observed that the smaller branches of the pulmonary artery which lie in close proximity to small bronchi receive fibers from the nerve plexus around the latter. The results of recent physiological experiments of Carlson and Luckhardt (1920) indicate that, at least in Amphibia and reptiles, these fibers are derived mainly, if not entirely, from the vagus outflow.

INNERVATION OF THE VISCERAL PLEURA.

According to Larsell (1923), the nerves which supply the visceral pleura emerge from the plexus on the pulmonary arteries near the hilum of the lung. They enter the pleura and run for some distance as fairly compact bundles and then break up into smaller bundles. The nerve fibers are distributed mainly to the pleura near the margins of the pulmonary lobes, particularly on the inner surfaces of the lobes. The pleura on the exposed surfaces of the lobes is but meagerly supplied by nerve fibers. Larsell found nerve fiber terminations in the visceral pleura mainly at the margins of the lobes. They were most abundant at the dorsal margin near the hilum. He found none on the caudal or caudo-ventral margins. In the rabbit the fiber terminations in the visceral pleura are small and of simple structure, but in the dog they are larger and more complex. They probably are receptive in function. The results of

degeneration experiments on rabbits reported by Larsell, though not conclusive, strongly suggest that the nerve fibers distributed to the visceral pleura are mainly components of the dorsal roots of the upper thoracic nerves, and reach the lung via the upper thoracic and inferior cervical sympathetic ganglia.

PULMONARY REFLEXES.

Direct Bronchial Reflexes.—The afferent fibers supplying the respiratory tract play an important rôle in the reflex control of normal respiratory rhythm. This will be discussed in succeeding paragraphs. Direct reflexes involving the tracheal and bronchial musculature which are initiated by stimulation of these afferent fibers also play an important rôle in the respiratory processes. Irritation of any part of the tracheal or bronchial mucosa elicits reflexes which involve the musculature of the respiratory tract either in whole or in part. As pointed out by Larsell (1921), the sensory nerve terminations situated at the openings into the respiratory portion of the lung differ somewhat morphologically from those situated in the mucosa of the larger bronchi. Whether or not these sensory terminations differ functionally is problematical. It seems not improbable, as was suggested by Larsell, that the afferent terminations in the larger bronchi represent a type of tactile terminations which is stimulated by masses of mucous or foreign particles within the bronchi. The reflex contraction of the bronchial musculature elicited by such stimulation would tend to prevent the displacement of matter in the respiratory passages distalward. Furthermore, such stimulation might elicit reflex coughing to expel the extraneous matter. The sensory terminations situated at the openings of the respiratory portion of the lungs might conceivably also serve the purpose of guarding against the entrance of foreign matter into the atria and air sacs by eliciting reflex constriction of the muscle bands at the openings of the alveolar ducts into the atria. As Larsell also suggested, however, they seem to be better adapted, by reason of their structure, to react to pressure stimuli than to touch. Although they may mediate impulses which elicit direct bronchial reflexes, they probably are stimulated by partial collapse of the lungs at each expiration and mediate impulses which are involved in the reflex control of respiratory rhythm.

The visceral pleura has quite generally been regarded as insensitive to stimulation (Capps, 1911; Hoffmann, 1920). Larsell (1928) elicited respiratory reflexes in decerebrated dogs by inflating a small rubber balloon placed between the lobes of the lung. These reflexes involved inhibition of the inspiratory movement and initiation of the expiratory blast. On the basis of his results, he concluded that

the nerve endings in the visceral pleura on the interlobar surfaces of the lung were stimulated by mechanical contact. He also expressed the opinion "that the nerve endings in the pleura are normally stimulated by the contact of adjoining interlobar surfaces during extreme inflation of the lung, although such stimulation probably occurs but rarely, if ever, in normal respiration with intact vagus nerves."

Bronchoconstrictor Fibers.—In view of the composition of the tracheal and bronchial musculature, changes in the length of the respiratory tubes can hardly be brought about by muscular contraction. By reason of the elasticity of the cartilage rings in the trachea and larger bronchi, these tubes tend to assume a maximum diameter, but the tonus of the tracheal and bronchial muscles normally imposes on these cartilage rings a certain degree of tension. This tonus, as indicated by the results of physiological experimentation, is mediated through the parasympathetic nerves. Section of the vagi results in dilatation of both the trachea (Einthoven, 1892) and bronchi (Weber, 1914). Stimulation of the peripheral end of the vagus, if the nerve is cut proximal to the origin of its recurrent branch, elicits diminution in the caliber of both the trachea and bronchi. When either vagus nerve is stimulated in this manner, diminution in the caliber of the bronchi is most marked on the homolateral, but is also apparent on the contralateral side. This result indicates that some vagus fibers normally cross over and enter the pulmonary plexus on the opposite side. In the cat, the extent of the crossing varies widely. In some animals, practically all the vagus fibers supplying the bronchioles are derived from the opposite side; in others nearly all of these fibers are derived from the same side. Crossing of a certain percentage of the bronchoconstrictor fibers seems to be the rule rather than the exception (Dixon and Ransom, 1912).

Powerful excitation of the cervical sympathetic in the cat, according to Dixon and Ransom, sometimes results in bronchoconstriction. Conversely, vagus stimulation occasionally elicits bronchodilatation. These results are unusual. They probably occur only in cases in which some sympathetic fibers are incorporated in the vagus and some vagus fibers in the cervical sympathetic.

Bronchodilator Fibers.—The bronchodilator fibers are sympathetic and arise mainly in the inferior cervical and first thoracic ganglia. The preganglionic fibers involved are components of the upper three thoracic nerves. Stimulation of the thoracic end of the cut cervical sympathetic trunk commonly results in bronchodilatation on one or both sides. The reaction is more marked, however, when the stimulus is applied to the upper thoracic rami. The bronchodilator fibers also have a bilateral distribution. In some cases, according to Dixon and Ransom, the sympathetic supply to

the bronchioles is derived almost entirely from the opposite side; in others the crossing of these fibers is less complete. The crossing of a certain percentage of the sympathetic fibers supplying the bronchi seems to be the rule rather than the exception. These findings of Dixon and Ransom regarding the bronchodilator fibers have, in general, been corroborated by the recent findings of Le Blanc and Van Wyngaarden (1924).

Afferent Stimulation and Bronchomotor Reflexes.—Bronchoconstriction may be elicited reflexly by a variety of afferent stimuli, *e. g.*, irritation of the mucous membrane of the nose and larynx. Dixon and Ransom (1912) found that reflex bronchoconstriction could be elicited by stimulation of the central ends of various nerves. In their experiments, stimulation of the central end of one vagus nerve, while the other remained intact, was very effective. They also elicited bronchoconstriction by stimulation of the central ends of the thoracic sympathetics, the central ends of the accelerator nerves connected with the inferior cervical ganglion and the central ends of the communicating rami of the second and third thoracic nerves. In no case did they observe bronchoconstriction after section of both vagi.

Bronchodilator reflexes are readily elicited by stimulation of the central end of one or both vagus nerves when both are severed. Consequently, the vagi contain afferent bronchodilator fibers. These reflexes are not abolished by section of the cervical sympathetic trunks, but are abolished by section of the spinal cord in the upper cervical region or section of the bronchial nerves arising from the inferior cervical and first thoracic ganglia. These facts suggest that reflex bronchodilatation involves a center in the medulla and that the reflexes are carried out through the white rami of the first, second and third thoracic nerves (Dixon and Ransom, 1913).

Action of Adrenalin and Atropin.—According to the current conception of the action of adrenalin, it should, if the bronchodilator fibers belong to the sympathetic system, cause profound bronchodilatation. Such indeed is the case. That adrenalin relieves bronchospasm in patients suffering from bronchial asthma is a common clinical observation. Januschke and Pollock (1909) showed, in both decerebrated and ether anesthetized cats, that adrenalin causes slight dilatation of the bronchioles, but, if by the use of a drug, *e. g.*, muscarin, the bronchioles were first thrown into a condition of tonus, adrenalin produces profound bronchodilatation. Trendelenburg (1912) also found that adrenalin caused marked relaxation of the muscle in an isolated ring of a bronchus. In experiments on cats, Dixon and Ransom found that whenever the bronchioles are not fully relaxed adrenalin causes a maximal active bronchodilatation. On the other hand, atropin brings about a

passive bronchodilatation by reason of its paralytic action on the parasympathetic terminations.

Innervation of the Pulmonary Vessels.—On the basis of the anatomical findings referred to above, it may be stated that the pulmonary vessels are supplied by both sympathetic and parasympathetic nerve fibers. That the sympathetic nerves to the lungs contain vasoconstrictor fibers has long been known. These fibers, probably, are distributed mainly to the bronchial vessels. The presence of pulmonary vasodilator fibers in the vagus was suggested by certain data advanced by Henriques (1892), but the results of later investigations failed to corroborate his findings. By a careful study of the simultaneous records of pressures in the aorta and a branch of the pulmonary artery, Bradford and Dean (1894) were led to conclude that the pulmonary vessels probably are supplied by vasoconstrictor fibers of sympathetic origin. They stated, however, that the effects obtained on the pressure in the pulmonary artery by sympathetic stimulation are relatively and absolutely small as compared with the vasomotor effects on the systemic vessels. Similar results have also been obtained by other investigators. On the basis of results obtained by the use of another method, Brodie and Dixon (1904) were led to an opposite conclusion. They maintained an artificial circulation through the lungs and measured the rate of flow when the nerves supplying the lungs were stimulated. Under the conditions of their experiments, the rate of flow was not altered by stimulation of either the vagus or sympathetic nerves. On the basis of this result, they concluded that neither the vagus nor sympathetic nerves convey vasomotor fibers to the pulmonary vessels. The fact that they were able to elicit vasomotor effects in similar perfusion preparations of other organs (intestine) by stimulation of the vagus and sympathetic nerves, strengthened this conclusion. It was further supported by the fact that certain drugs (adrenalin, pilocarpin, muscarin) which cause marked vasoconstriction in the intestine had no effect, in their experiments, on the pulmonary vessels. According to Plumier (1904), the outflow from a perfused lung is diminished by sympathetic stimulation and also by the use of adrenalin in some cases. Hall (1923) reported visible constriction of the arterioles in the cat's lung, as observed microscopically by the method of transillumination, when adrenalin was added to the circulating blood. Le Blanc and Van Wyngaarden (1924) also claimed to have demonstrated, in perfusion preparations of the cat's lung, that the same vagus stimulation which elicits bronchoconstriction also elicits pulmonary vasodilatation. They also obtained results which seemed to indicate the existence of pulmonary vasoconstrictor fibers in the sympathetic nerves to the lungs. On the basis of these findings, they concluded that the vagus supply to the lungs includes both

bronchoconstrictor and vasodilator fibers, and the sympathetic supply both bronchodilator and vasoconstrictor fibers. Dixon and Hoyle (1928) once more studied the effect of stimulation of the vagus and sympathetic nerves on the pulmonary vessels, under carefully controlled experimental conditions. They observed the effects of nervous stimulation on the pulmonary arteries, as compared with its effect on the heart and systemic arteries, in the intact animal under anesthesia. The results of their study afforded absolutely no evidence of an effective vasomotor supply to the pulmonary system.

In view of the conflicting data regarding the vasomotor innervation of the pulmonary vessels, it probably is safe to conclude that direct vasomotor influences play no important rôle in the regulation of the blood flow through the pulmonary system. This system is complete in itself and differs from the systemic circulation chiefly in that the capillary resistance is much smaller. Consequently, the arterial pressure is lower and the velocity of the blood flow greater in the pulmonary than in the systemic circuit. In view of the mechanical conditions which prevail, it must be apparent that the regulation of pulmonary circulation is largely mechanical and depends in a large measure on the regulatory control of the systemic circulation.

Bronchial Neuroses.—In view of the reactions of the bronchi and bronchial vessels to both direct and reflex vagus and sympathetic stimulation, it is clear that disturbances of the pulmonary innervation might result in asthmatic conditions. It is improbable, however, that all forms of bronchial asthma are to be regarded etiologically purely as neuroses. In many instances the pathological nervous manifestations associated with asthmatic conditions probably represent the result of catarrhal inflammations of the bronchial mucosa. On the other hand, inflammatory conditions of the bronchial mucosa may, under certain conditions, arise as manifestations of a primary disturbance of the bronchial innervation. In any case, asthmatic conditions involve profound disturbances of the bronchial innervation.

That asthmatic attacks may be brought about by reflex stimulation of various afferent nerves, *e. g.*, the afferent fibers supplying the nasal mucosa, is well known. Likewise, strong emotional disturbances are not infrequently accompanied by bronchospasm. The so-called sexual asthmas, *i. e.*, asthmatic attacks which follow disturbances of the sexual apparatus, must also be regarded as manifestations of reflex stimulation. That the more severe attacks of asthmatic women regularly coincide with their menstrual periods is a fact of common clinical observation. To what extent internal secretory processes play a rôle in asthmatic conditions associated with sexual disturbances is not known. That they are essentially

reflex nervous manifestations cannot be doubted. In these, as in other asthmatic conditions which are brought about by reflex nervous stimulation, hyperirritability of the bronchoconstrictor apparatus must be regarded as an important factor.

REFLEX REGULATION OF RESPIRATORY MOVEMENTS.

Respiratory Nerves.—Although respiration is a vegetative function, the respiratory movements in mammals involve extensive somatic nervous mechanisms. The somatic nerves involved are essentially voluntary, yet the respiratory movements are carried out automatically and are subject to voluntary control only within well-defined limits.

The most important somatic nerve of respiration is the phrenic, which arises from the third, fourth and fifth cervical spinal nerves and supplies the diaphragm. The spinal accessory nerve and branches of the cervical and brachial plexuses innervate the neck and shoulder muscles which are concerned in respiration. The intercostal nerves innervate the muscles of the thorax and abdomen. A branch of the facial nerve innervates the muscles of the nose and branches of the vagus supply the muscles of the larynx. All these muscles belong to the somatic system, and their innervation is essentially somatic. Although it has been shown that skeletal muscles are also innervated by sympathetic nerves (Chapter XV), none of the muscles involved in the respiratory movements, except possibly the muscles of the diaphragm, has a special sympathetic nerve supply.

That the phrenic nerve includes sympathetic fibers in relatively large numbers has long been known. They are derived mainly from the middle and inferior cervical ganglia. In cross-sections of the phrenic nerve they appear grouped in bundles, mainly at or near the periphery (Felix, 1922). Many of the sympathetic fibers incorporated in the phrenic nerve pass out in its cervical and thoracic branches, but a goodly proportion remains in its diaphragmatic branches. On reaching the diaphragm, the phrenic nerve divides into numerous branches; some are distributed over the thoracic surface (subpleural branches), but most of them pierce the muscle and spread over the abdominal surface (subperitoneal branches). On the abdominal surface of the diaphragm some of the branches of the phrenic nerve communicate with the phrenic plexus. This plexus accompanies the inferior phrenic artery and is made up of fibers which are derived mainly from the cœliac plexus. At the junction of the phrenic nerve with the phrenic plexus, on the right side, is located a small ganglion (phrenic ganglion). Felix (1922) also described a considerable number of other small ganglia mainly in the lumbar parts of the diaphragm.

The motor innervation of the entire diaphragm seems to be supplied through the phrenic nerves. These nerves also supply afferent fibers to its entire central area. The border zone of the diaphragm is supplied by afferent fibers from the intercostal nerves (Felix, 1922). This anatomical finding is corroborated by clinical observations. Sensations of pain can be localized only in the costal portions of the diaphragm. Irritation of the central area of the diaphragm, like injury to the phrenic nerve, commonly manifests itself in characteristic shoulder pains. These pains probably are analogous with pains which result from irritation in a visceral organ, but which are localized in a somatic area, *i. e.*, they are typical referred pains. It may be assumed, therefore, that the afferent fibers conveyed to the diaphragm through the phrenic nerves, like the afferent fibers which supply the visceral organs through the sympathetic trunks, belong to the general visceral afferent system.

Sympathetic fibers are supplied to the diaphragm in considerable abundance. Many of these fibers probably are distributed to the diaphragmatic muscles, but they do not mediate diaphragmatic movements. The sympathetic innervation of the diaphragmatic muscles probably subserves the same function as the sympathetic innervation of other skeletal muscles. The functional significance of the sympathetic innervation of skeletal muscles will be discussed in Chapter XV.

The Respiratory Center.—The coördinated activity of the extensive mechanisms involved in the respiratory movements early suggested the existence of a respiratory center in the central nervous system. On the basis of early experimental studies, this center seemed to be located at the level of the calamus scriptorius. The results of more recent investigations have demonstrated that the respiratory center is bilateral and that each lateral portion lies some distance from the median plane at the general level of the calamus. A vertical section of the medulla in the median plane does not interfere with normal respiration. Transverse section of the spinal cord above the origin of the phrenic nerves results in immediate cessation of all respiratory movements except those of the nose and larynx. Section of the brain stem above the respiratory center does not result in cessation of respiration. This center has been delimited only by physiological experimentation. No special cell groups have been found which are sufficiently distinct anatomically to warrant the conclusion that they constitute the center in question.

The respiratory center stands in close relation to the nuclei of termination of the vagus, and receives afferent impulses through this nerve from various parts of the respiratory tract as well as other areas of vagus distribution. It is also functionally connected with other afferent nerves. The efferent fibers which convey impulses from the respiratory center to the motor nuclei of the respiratory

nerves probably run in the anterior part of the lateral funiculus. Whether the efferent chains from the respiratory center to the spinal motor nuclei are made up of one or a series of neurons is not known. In order to account for the regular rhythmic respiratory movements, it is necessary to assume that impulses arising in the respiratory center are distributed through these efferent fibers in a coördinated manner to the lower motor nuclei of the cord and the motor nuclei of the facial and vagus nerves, thence to be conveyed to the respiratory muscles.

Reflex Stimulation of the Respiratory Center.—As stated above, stimulation of the afferent fibers of the vagus and certain other peripheral nerves elicits reflex responses of the bronchial musculature. Likewise, stimulation of any afferent nerve may affect the rate or amplitude of the respiratory movements. Emotional states also are not infrequently accompanied by change in respiration. It has also been shown experimentally that stimulation of certain portions of the cerebral cortex and brain stem affect the respiratory center. We may assume, therefore, that afferent fibers of perhaps all of the cranial and spinal nerves mediate impulses which are conveyed to the respiratory center, and that this center is also influenced by impulses which arise in the cerebrum and are conveyed downward in the brain stem. Stimulation of afferent nerves affects the activity of the respiratory center in various ways. The respiratory rate may be changed together with an increase or a decrease in amplitude, the inspirations and expirations may each be increased or decreased, or one phase may be modified to a greater degree than the other. Under experimental conditions, however, stimulation of an afferent nerve which contains cutaneous fibers usually results either in acceleration, manifested by quicker and stronger inspirations and active expirations, or inhibition, manifested by slower and more feeble respiratory movements or complete cessation of respiration. Whether afferent impulses which augment and those which inhibit the respiratory movements are conveyed by the same or different afferent fibers is not definitely known. It is highly probable that the afferent fibers which mediate these impulses also subserve other functions, *e. g.*, the ascending fibers in the spinal cord and brain stem which receive cutaneous impulses from the peripheral afferent neurons and convey them to the thalamus, whence they are relayed to the cerebral cortex, may through collaterals also affect the respiratory center.

The afferent fibers of the vagus, particularly those which are distributed along the respiratory tract, sustain a peculiarly intimate functional relationship to the respiratory center. The normal physiological effect of afferent vagus stimulation is inspiratory inhibition. This is readily demonstrated by the effect of gradually cooling both vagi until they cease to conduct. By reason of the

absence of inhibitory impulses under these conditions, inspiration is both lengthened and deepened; expiration, however, is not appreciably altered. A like result may be obtained by extirpation of the inferior colliculi. Bilateral vagotomy combined with this operation results in inspiratory spasm. It appears, therefore, that the inferior colliculi include a center which exerts an inhibitory influence on the respiratory center and functions concurrently with vagus stimulation.

Section of both vagi in the neck alone immediately alters the character of the respiratory movements. The rate is retarded and the amplitude is increased. The inspirations become longer and deeper and are followed by an appreciable pause. Section of only one vagus may result in an intermediate effect, *i. e.*, the respiratory rate is retarded somewhat and inspiration is slightly deepened. This is not a temporary effect, but lasts for a considerable period. It may be assumed, therefore, that some influence which normally maintains the respiratory movements at a more rapid rate has been cut off. This influence consists in the tonic action on the respiratory center of the afferent vagus fibers which are distributed to the lungs, and constitutes one of the major factors in the maintenance of normal respiratory rhythm. When these vagus fibers are severed the respiratory center drops into a slower, unregulated rhythm. According to Hering and Breuer, expansion of the alveoli during inspiration gives rise to vagus impulses which depress the respiratory center and result in inhibition of inspiration. Hering and Breuer expressed the opinion that the impulses which excite inspiration are mediated by a special group of vagus fibers. According to Einthoven (1908), the collapse of the lungs on expiration gives rise only to very weak action currents in the vagus nerve. Neither is it necessary to assume that normal inspiration requires vagus stimulation. Inspiration is the natural function of the respiratory center and it may well be that cessation of the inhibitory influence of vagus stimulation is sufficient to release the inspiratory impulses which were held in abeyance during expiration. Stimulation of the central end of the divided vagus affects the respiratory center in a variety of ways, depending on the strength of the stimulus and the condition of the center. Such stimulation usually inhibits the respiratory movements partially or completely, resulting either in smaller movements or complete cessation of respiration with the thorax in the condition of passive expiration. On the other hand, the rate of the respiratory movements may be increased until respiration ceases with the thorax in an inspiratory position and the inspiratory muscles in a state of tetanic contraction. These two main effects of stimulation of the central end of the vagus are commonly interpreted as indicating that the afferent vagus fibers which are distributed to the lungs are of two kinds, each of which has a specific effect on the vagus center, *i. e.*, there are: (1) inspira-

tory fibers, whose influence tends to increase the rate of respiration by increasing the rate of inspiratory discharge from the respiratory center, and (2) expiratory (or inspiratory inhibiting) fibers, whose influence tends to retard the rate of respiration by inhibiting the inspiratory discharges from the respiratory center either partially or completely. This interpretation does not militate against the theory that normal inspiration is a function of the respiratory center which does not depend on afferent vagus impulses.

Normal quiet expiration may be regarded as a purely passive process. The inspiratory muscles are relaxed and the displaced masses return to a resting position by reason of the force of gravity and the normal elasticity of the tissues involved. The collaboration of the lungs themselves in this process is augmented by their almost ideal elasticity which becomes effective as soon as the intrathoracic pressure begins to rise following inspiration. On the other hand, under conditions of physical exertion or dyspnea, passive expiration no longer suffices and expiration, though still automatic, becomes an active process.

In view of the close coördination of inspiration and expiration, particularly when expiration becomes an active process, it seems highly probable that there are special cells, probably located in the reticular formation in the region of the inspiratory center, whose special function is the regulatory control of expiration when such control is required. These cells probably are activated only by stronger stimuli than are required to activate the cells which normally control inspiration. The evidence available at present does not warrant the assumption of a separate expiratory center.

Respiratory Reflexes From the Upper Air Passages.—Stimulation of the sensory fibers supplying the nasal mucosa (trigeminal) by injurious or irritating gases elicits reflex inhibition of respiration. A similar effect may be obtained by stimulation of the sensory fibers supplying the pharynx (glossopharyngeal). Indeed, every act of swallowing elicits temporary inhibition of respiration through the glossopharyngeal nerve. The laryngeal mucosa is supplied by sensory fibers of the superior laryngeal nerve. Stimulation of this nerve also elicits respiratory inhibition. This reflex inhibition of respiration elicited by stimulation of the sensory fibers distributed along the upper air passages may be regarded as a reaction which automatically protects the lungs from injurious gases. The protective character of this reaction is further evidenced by the fact that reflex closure of the larynx occurs simultaneously with the cessation of respiration and, if the stimulation is strong enough, the bronchial musculature also contracts, so that the passage to the alveoli is made still more difficult. Although this reflex cessation of respiration is only temporary, it is automatic, and affords at least

a short interval before the inhibition is broken through by the increasing irritability of the respiratory center, during which the individual may escape from a dangerous locality. In certain animals, *e. g.*, certain of the water birds, reflex inhibition of respiration may be maintained for relatively long intervals. Doubtless, this is a special adaptation of the reflex to meet the needs of diving. That irritating gases or foreign bodies which enter the larynx may cause reflex coughing is a fact of common experience. This may be regarded as an automatic but purposeful attempt to expel the stimulating object. In the act of coughing the rima glottis which shortly before was closed is forced open by a sudden explosive expiration. This involves not only reflex inhibition of the inspiratory movements, but also reflex excitation of expiratory movements of a peculiar type. The coughing reflex may be elicited by stimulation of the vagus fibers distributed to any part of the respiratory tract (Staehelin, 1914). It is not elicited from all the areas of vagus distribution in the respiratory tract with equal facility. Stimulation of the deeper parts of the larynx is most effective. The facility with which this reflex is elicited gradually decreases approaching the smaller subdivisions of the bronchial tree. It is also rarely elicited by irritation of the pharynx and the base of the tongue. On the other hand, the coughing reflex may be elicited by stimulation of the afferent vagus fibers supplying various visceral organs, *e. g.*, the liver and spleen. It has also been observed clinically that under certain conditions irritation of the parietal pleura elicits the coughing reflex.

Sneezing may also be regarded as a protective respiratory reflex. In this instance the posterior nares just previously closed by contraction of the superior constrictor muscles of the pharynx is forced open by explosive expiration. This reflex is elicited most commonly by stimulation of the afferent fibers (trigeminal) supplying the nasal epithelium. It serves to remove mucus or other extraneous matter from the nasal mucosa.

Other Special Respiratory Reflexes.—Yawning is in part a respiratory reaction which may be regarded as a type of indirect vascular reflex which serves the purpose of improving the circulation (Regelsberger, 1924). Simultaneous stretching reflexes not uncommonly aid in this process. The stretching and yawning reflexes, according to Dumpert, are intimately associated in their phylogenetic origin. Man is able, therefore, only by practice to separate these two reflexes and to suppress the stretching reflex entirely. It is interesting to note in this connection that not uncommonly in cases of hemiplegia yawning is accompanied by forced stretching movements in the paralyzed limbs. This suggests the primitive origin of the reflexes and their incorporation in the reflex pattern of

the older parts of the brain. The frequent occurrence of yawning in cases of brain tumor and encephalitis also suggests the primitive origin of this reflex.

Sobbing, laughing and weeping also involve forced automatic movements, particularly of the larynx and diaphragm, which affect respiration and in general are coördinated with the movements of expression. These reflexes are elicited by emotional states. Although they may, in most instances, be inhibited voluntarily in greater or less degree, they are carried out through centers which are essentially automatic.

Hiccough is a respiratory reflex which is purely automatic and, in general, not subject to voluntary inhibition. The familiar phonation accompanying this reflex is inspiratory. It is caused by suction of air past the just closing vocal folds by spastic contraction of the diaphragm. The diaphragmatic movement consists essentially of a short sudden beat. The afferent impulses are commonly conveyed by afferent fibers in the phrenic nerve, but the stimuli which elicit this reflex are obscure. Hiccough may arise without any apparent cause and persist for a short or a long interval. Transient hiccough may be regarded as a harmless disturbance of respiration, but when hiccough persists for a relatively long time, as it not infrequently does in certain pathological conditions, it becomes a matter of grave clinical importance by reason of its effect on the general physical condition of the patient.

Hiccough is not infrequently caused by irritation of the phrenic nerve. It occurs commonly in cases of aortic aneurism, carcinoma in the region of the root of the lung and in all affections of the diaphragm. It frequently occurs also in cases of peritonitis and carcinoma of the stomach, liver, kidney, or adrenal gland. It has also been reported in operations for hernia. Hiccough probably is always a reflex phenomenon. Regelsberger (1924) has pointed out that the stimuli which elicit this reflex may arise throughout the entire area of distribution of the phrenic nerve and the sympathetic fibers connected with this nerve. Doubtless, the phrenic nerve plays a major rôle in the afferent conduction of these impulses. Certain other afferent nerves must also mediate such impulses, since there are no data available which indicate a distribution of afferent phrenic fibers, through the sympathetic plexuses below the diaphragm, to any of the abdominal organs.

In certain cases hiccough arises, not as a reflex phenomenon, but as a result of stimuli arising in the blood, *e. g.*, in cases of uremia, acetoneuria, and venous stasis in the region of the medulla oblongata. Obviously, in such cases certain cells in the brain stem react to tonic substances in the blood. Hiccough may also arise as a result of psychic disturbances and in cases of organic diseases of the central

nervous system. The existence of a special center in the brain which mediates this peculiar respiratory phenomenon seems improbable. It probably is carried out through the general respiratory center.

The Chemical Regulation of Respiration.—Although reflex stimulation plays an important rôle in the regulatory control of the respiratory movements, the respiratory center is constantly influenced by chemical stimulation. The results of experimental studies have amply demonstrated that the respiratory rhythm varies with variations in the O_2 and CO_2 content of the blood. A decrease in the ratio of O_2 and CO_2 in the blood is commonly accompanied by an increase in the rate or force of the respiratory movements or both. On the contrary, an increase in the ratio of O_2 to CO_2 in the blood is accompanied by retardation of the respiratory movements. In general, the activity of the respiratory center varies inversely as the ratio of the O_2 to the CO_2 content of the blood. It does not follow, however, that the respiratory center is stimulated directly by either oxygen or carbon dioxide. Nor does it react directly to changes in the hydrogen-ion concentration of the blood. The weight of experimental evidence at present favors the theory that the chemical control of respiration depends on the acid-base balance of the respiratory center.

The various discordant hypotheses regarding the chemical control of respiration were brought into harmony by Gesell (1925) when he pointed out that the hydrogen-ion concentration of the respiratory center itself is the true respiratory hormone. According to his theory, pulmonary ventilation is determined indirectly by the oxygen supply, since this determines the absolute and relative amounts of lactic acid and carbon dioxide formed in the living tissues, and controls the efficiency of transport and elimination of acid. "By virtue of its own metabolism and its extreme sensitivity to minute changes in its own hydrogen-ion concentration," according to Gesell, "the respiratory center is sensitive to minute changes in its own oxidations, and, therefore, to changes in the tension of the oxygen in the arterial blood. The capacity of the center to respond to changes in the arterial carbon dioxide tension consequent to fluctuations in the general metabolism, however, must also be a factor." On the basis of this theory, the chemical control of respiration may be regarded as involving mainly two sets of factors which influence the acid-base balance of the respiratory center, viz.: (1) the hydrogen-ion concentration of the blood and the volume of blood supplied to the center, and (2) the metabolic activity of the cells in the respiratory center.

CHAPTER IX.

INNERVATION OF THE DIGESTIVE TUBE.

EXTRINSIC NERVES OF THE DIGESTIVE TUBE.

Pharynx.—The pharynx derives its innervation from the glossopharyngeal, vagus, and sympathetic nerves. The glossopharyngeal supplies mainly the upper portion; the pharyngeal branches of the vagus, the middle and lower portions. Where the branches of the glossopharyngeal and vagus meet they enter into a plexus formation which, together with some of the sympathetic rami supplying the pharynx, constitutes the pharyngeal plexus. The sympathetic supply to the pharynx is derived mainly from the superior cervical ganglion. Some of the sympathetic fibers enter the pharyngeal plexus through separate sympathetic rami; others become incorporated in the pharyngeal branches of the vagus before reaching the pharynx, and join the plexus with these nerves. Still others pass directly to the pharyngeal musculature without taking part in the plexus formation. The majority of the sympathetic fibers seem to be distributed to the lower portion of the pharynx.

Esophagus.—The esophagus is supplied by the vagus and sympathetic nerves. The vagus supply to the cervical portion is derived from the recurrent nerve through parallel branches which enter the esophageal wall. In general, these branches neither cross the median plane nor enter into a plexus formation. In the thorax both vagi come into close relation to the esophagus and supply branches to it. Furthermore, two or three branches of the right vagus commonly join the left at this level. The distribution of each vagus nerve to the thoracic portion of the esophagus is not confined to its own side, but each nerve also sends branches to the opposite side. In general, the left vagus supplies the anterior surface and the right vagus the posterior surface of this portion of the esophagus.

The sympathetic nerves supplying the esophagus arise mainly from the inferior cervical ganglion. Some fibers arising in the cervical sympathetic ganglia also reach the esophagus through communications of the cardiac nerves with the recurrent branch of the vagus. The lower portion of the esophagus also receives rami from the thoracic portion of the sympathetic trunk. In general, one or more rami arising from the stellate ganglion join the recurrent nerve; others either join the vagus trunk or pass directly to the esophagus. Some of the thoracic rami pass directly to the esophagus;

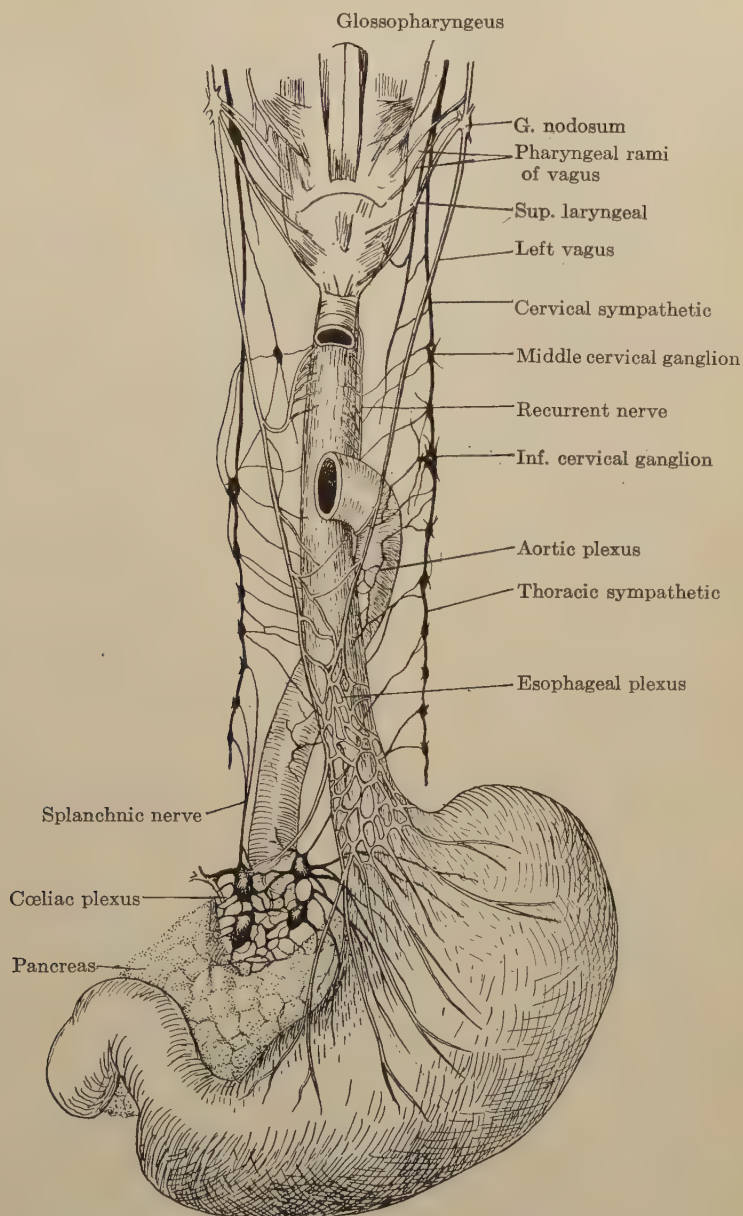


FIG. 39.—Diagrammatic illustration of the extrinsic nerves of the pharynx, esophagus, and stomach.

others join the aortic plexus and supply fibers to the esophagus through this plexus. Sympathetic fibers also reach the esophagus via the greater splanchnic nerve. In the posterior mediastinum the sympathetic nerves and the vagi with their intercommunicating branches constitute a plexus surrounding the esophagus (esophageal plexus). Branches arising from this plexus penetrate the esophageal wall.

Stomach.—The stomach is also supplied by the vagus and sympathetic nerves. From the esophageal plexus, both vagi continue along the esophagus, the left on its anterior and the right on its posterior surface. On approaching the stomach, both vagi commonly break up into three main divisions, viz.: a left, a middle, and a right division. As the left vagus passes down over the anterior aspect of the stomach, its left division supplies branches to the fundus and approximately the upper two thirds of the corpus; its middle division supplies the prepyloric region; its right division passes to the liver. As the right vagus passes down over the posterior aspect of the stomach, its left division supplies the cardia, the lesser curvature, and a greater or lesser portion of the corpus; its middle division supplies the prepyloric region; its right division joins the right celiac ganglion. Not infrequently branches of both vagi anastomose and form a plexus at the right side of the cardia from which fibers are supplied to the cardiac region. In the prepyloric region branches of the middle division of both vagi enter the hepato-gastric ligament.

In the hepato-gastric ligament and a few centimeters from the subcardial portion of the lesser curvature of the stomach, sympathetic fibers derived from the celiac plexus and vagus fibers mingle with each other and together approach the stomach to be distributed mainly to the subcardial and prepyloric regions. These fibers do not form an intricate plexus, but, in general, bundles of vagus and sympathetic fibers run parallel to each other. In addition to these mixed nerves, unmixed sympathetic rami derived from the celiac plexus also join the stomach (Brandt, 1920).

Small Intestine.—The small intestine, like the stomach, is innervated by both vagus and sympathetic fibers. The vagus supply to the intestine is derived mainly from the right vagus through the division of that nerve which joins the celiac plexus. The sympathetic fibers are derived mainly from the celiac and superior mesenteric plexuses. Both sets of fibers enter the small intestine through the mesenteric nerves, which, in general, accompany the mesenteric arteries. Vagus and sympathetic fibers can be distinguished from each other by differences in caliber and their distribution in the intestinal wall. After leaving the celiac plexus the vagus fibers form bundles, which either run free in the mesentery or along the larger blood vessels and usually enter the intestinal wall with the

latter. These fiber bundles have no essential connections with the vessel walls, although they may run parallel to the vessels throughout a part or all of their course. They penetrate the subserosa and longitudinal muscle layer and enter the myenteric plexus. The sympathetic nerves are, in general, more intimately associated with the mesenteric vessels. They anastomose freely in the subserosa. Most of the fibers enter the intestinal wall in close connection with the adventitia of the larger vessels; others form a plexus in the subserous layer. The latter probably are mainly general visceral afferent fibers.

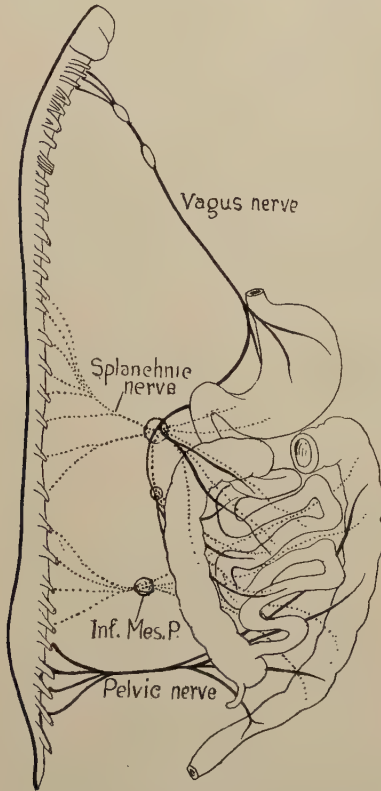


FIG. 40.—Diagram illustrating the distribution of sympathetic and parasympathetic nerves to the stomach and intestine.

Large Intestine.—The cecum, vermiform appendix, and ascending and transverse portions of the colon are supplied by nerves which arise directly from the superior mesenteric plexus. These nerves include both vagus and sympathetic fibers. The descending colon and upper part of the rectum are supplied by nerves which arise from the inferior mesenteric plexus. This plexus is a derivative of

the aortic plexus, through which it also receives vagus fibers from the coeliac plexus. Therefore, the nerves supplying the descending colon, at least in man, include both vagus and sympathetic fibers. The portion of the large intestine supplied by vagus fibers varies somewhat in different animals. The lower part of the rectum is supplied by sympathetic fibers derived from the upper and lower divisions of the hypogastric plexus. These fibers accompany the superior and middle hemorrhoidal arteries. The rectum is also supplied through the white rami of the second, third, and fourth sacral nerves and the pelvic plexus. The inferior hemorrhoidal branches of the pudendal nerve (third and fourth sacral) also supply fibers to the lower part of the anal canal and the external sphincter.

INTRINSIC NERVES OF THE DIGESTIVE TUBE.

General Morphology.—The intrinsic nerve supply of the digestive tube (enteric nervous system) consists mainly of the myenteric plexus situated between the longitudinal and circular muscle layers, and the submucous plexus situated in the submucosa. Various authors (Openchowsky, 1889; Worobiew, 1910, 1913; Kondratjew, 1928; and others) also described a subserous plexus, particularly in the stomach. This subdivision must, however, be regarded as somewhat artificial. Both the myenteric and submucous plexuses include numerous ganglia which are intimately connected with each other by strands of nerve fibers. These strands are made up largely of fibers which arise in the ganglia, but they also contain fibers which enter the wall of the digestive tube through its extrinsic nerves. The two plexuses are connected with each other by numerous strands of nerve fibers, which include both fibers which arise in the myenteric and submucous ganglia, and fibers which enter the digestive tube through its extrinsic nerves. According to the current teaching, the efferent components of the vagus and sacral nerves which enter the wall of the digestive tube are preganglionic neurons which effect synaptic connections with neurons in the enteric ganglia. These nerves, with the enteric plexuses, constitute the parasympathetic innervation of the digestive tube. The sympathetic components of the nerves which enter the wall of the digestive tube are postganglionic fibers. They do not effect synaptic connections with enteric neurons, but terminate directly in relation to the tissues which they innervate. As an exception to this general plan of efferent innervation, Langley (1913) reported that in the rabbit, following the administration of nicotin in doses sufficient to abolish the effect of stimulation of the vagus and pelvic nerves, stimulation distal to the pelvic plexus always resulted in contraction of the large intestine. He concluded, therefore, that some of the preganglionic fibers in the sacral nerves effect synaptic

connections with neurons in the pelvic plexus, *i. e.*, outside the intestinal wall. Visceral afferent fibers of both vagus and spinal origin also reach the digestive tube via its extrinsic nerves. These fibers merely traverse the enteric plexuses, but do not enter into synaptic relationship with enteric neurons.

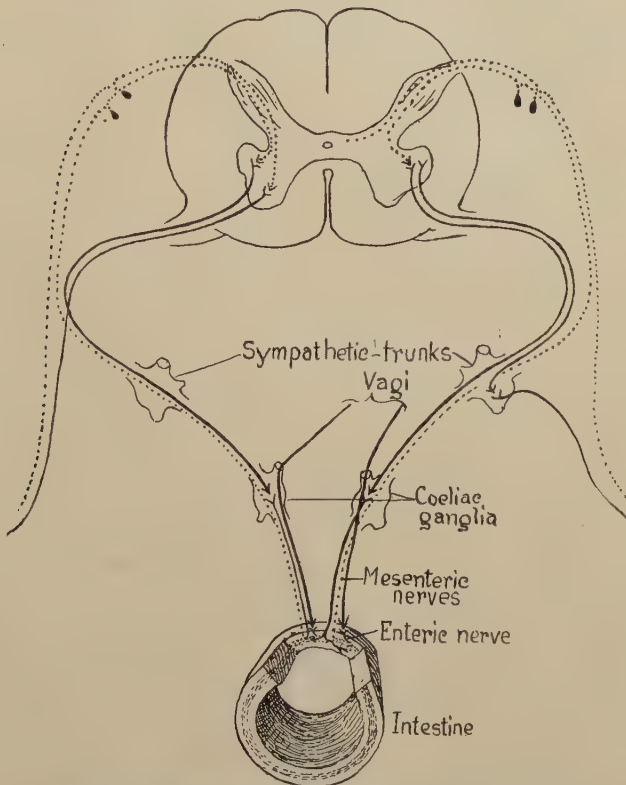


FIG. 41.—Diagram illustrating preganglionic and postganglionic fibers in the sympathetic and vagus efferent chains to the intestine.

Structure and Relationships of the Enteric Plexuses.—In the intestine the myenteric plexus is situated between the outer longitudinal and inner circular muscle layers and extends entirely around the tube. The fiber bundles are made up largely of unmyelinated fibers. They vary greatly in size and interlace and anastomose freely with each other. In general, the ganglia are located at the nodal points in the meshwork of fiber bundles. The ganglia also vary greatly both in size and in the number of their constituent neurons. They conform, in general, to the shape of the intermuscular spaces which they occupy. Many of them are distinctly flattened or lens-shaped. Viewed from the flattened surface, they

are usually somewhat angular in outline, depending on the number and arrangement of the fiber bundles associated with them. Not infrequently fibers arising in a ganglion may be traced for some distance in these fiber bundles. The majority of the fiber bundles seem to run from one ganglion to another and give off branches to the musculature. In preparations taken in the region of the mesenteric attachment, branches of the extrinsic nerves may be traced into many of the myenteric ganglia. Some of the fibers in these branches apparently terminate in the first ganglion entered; others pass through this ganglion into the rami which connect it with other ganglia in the myenteric plexus, or into a ramus which leads into the submucous plexus. Numerous rami may be traced from the myenteric plexus into the submucosa, where they join the submucous plexus (Kuntz, 1922). These rami usually arise at a nodal point or directly from a ganglion in the myenteric plexus and run between the bundles of circular muscle fibers into the submucous layer. They include both fibers of extrinsic origin and fibers which arise in the enteric ganglia.

The submucous plexus also extends entirely round the intestine in the submucous layer. The nerve complex which constitutes this plexus is not confined to a definitely delimited zone in the submucous layer. Some of the fiber bundles lie near the circular muscle layer; others lie close to the muscularis mucosæ. Mechanical separation of the mucosa and submucosa from the outer musculature, however, usually effectively removes the submucous plexus from the circular muscle layer.

The ganglia in the submucous, like those in the myenteric plexus, are usually located at nodal points. Some of them are distinctly flattened, but not to the same extent as the majority of the myenteric ganglia. Many of them are somewhat elongated and rounded or oval in cross-section. In many instances, a ramus which connects the submucous with the myenteric plexus may be traced into one of these ganglia where some of its fibers terminate; others merely pass through to continue farther in the submucous plexus. Nerve fibers may also be traced, either singly or in small bundles, from the submucous plexus to the muscularis mucosæ. Many of these fibers penetrate the muscularis mucosæ and ramify among the mucous glands or continue into the intestinal villi. Some of the latter supply the muscle fibers in the villi, others approach the intestinal epithelium and end in terminal ramifications among the epithelial cells (Kuntz, 1922; Hill, 1927).

The structure of the enteric plexuses has been studied less extensively in the large intestine than in the small intestine, but the anatomical data available indicate that it does not differ essentially, in this division of the digestive tube, from the structure exhibited by these plexuses in the small intestine.

The study of the structure of the myenteric plexus is rendered more difficult in the stomach than in the intestine by reason of the more complex arrangement of the musculature. According to Müller (1924), who cited the work of Baer and Brandt, the myenteric plexus in the stomach consists of a rich intermuscular meshwork of nerve fiber bundles in which groups of ganglion cells are incorporated. In preparations of the human stomach, ganglion cells were observed only in relatively small numbers in the submucous plexus.

The myenteric plexus presents the same structural features in the esophagus as in the intestine. In man, according to Greving (1920), the upper limit of the definitive plexus is about 3 or 4 cm. below the larynx. No ganglia have been observed in the esophageal wall above this level, although strands of nerve fibers which do not form a plexiform meshwork also occur between the muscle layers in the upper portion of the esophagus.

The submucous plexus in the esophagus exhibits a meshwork of nerve fiber bundles which, in general, contain fewer fibers than those in the myenteric plexus. According to De Witt (1900), and Sabussow (1913), who studied methylene-blue preparations of the esophagus in the cat and rabbit, the submucous plexus also contains groups of ganglion cells at its nodal points. Koslowsky (1900), who likewise studied methylene-blue preparations of the esophagus in the same animals, failed to find ganglion cells in the submucous plexus. Neither did Greving (1920) find ganglion cells in the submucous plexus in Bielchowsky preparations of the human esophagus. In view of the fact that ganglion cells occur in abundance in the submucous plexus throughout the intestine, and have also been demonstrated in the submucous plexus in the stomach, we see no reason, in spite of these negative findings, to discredit the positive findings of those investigators who have described ganglia in the submucous plexus in the esophagus.

The major portion of the submucous plexus in the esophagus lies so close to the muscularis that, in preparations in which the mucosa and submucosa have been separated from the muscularis mechanically, a large part of the plexus remains adherent to the inner surface of the circular muscle layer. This plexus is intimately connected with the myenteric plexus by numerous fiber bundles. Fibers may also be traced from it into the mucous epithelium, where they terminate among the epithelial cells. Many of the fibers which terminate in the esophageal epithelium are visceral afferent components of the vagi. Possibly, fibers which arise in the intramural ganglia may also terminate in the esophageal epithelium. This, however, has not been demonstrated.

No intrinsic plexuses have been described in the walls of the pharynx except the pharyngeal plexus which, as stated above, is

made up of glossopharyngeal, vagus, and sympathetic fibers. Many of the fibers which supply the pharyngeal mucosa and musculature traverse this plexus; others pass directly to these tissues without entering the plexus.

The Enteric Neurons.—The majority of the enteric neurons are multipolar, but bipolar and unipolar neurons have also been described in the enteric plexuses (Hill, 1927). As a result of very careful histological studies, based mainly on Bielchowsky preparations of the intestine of man and other mammals, Müller (1911) was able to show that the enteric neurons differ sufficiently in their

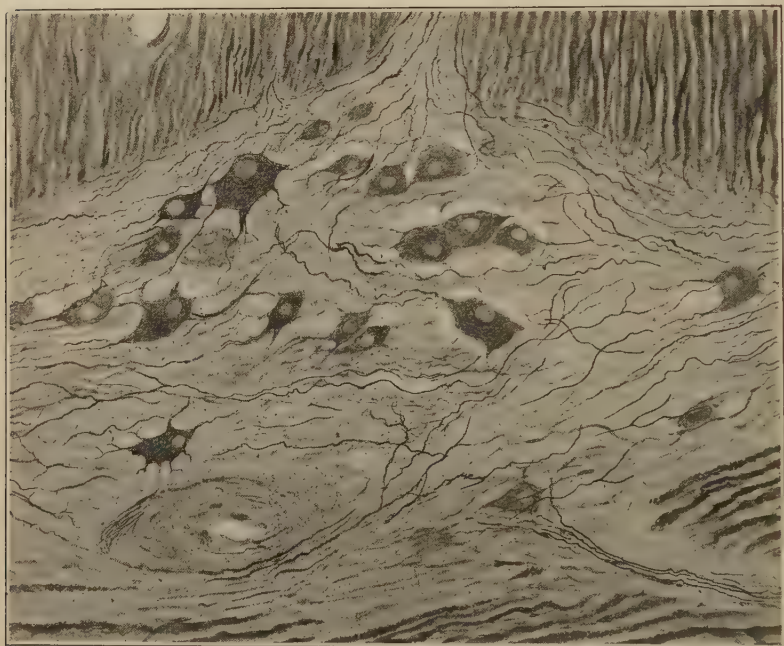


FIG. 42.—A ganglion in the myenteric plexus drawn from a tangential section of the intestine of the dog (pyridine silver).

morphological characters from the neurons in other parts of the autonomic system to set them off as a distinct type. This difference involves not so much the size and general structure of the cell body as it does the character, arrangement, and distribution of the dendrites, and the relation of the neurons to the adjacent tissues. In a more recent study involving measurements of the dimensions and comparison of the form and general structure of the cell bodies of neurons in the enteric ganglia and the ganglia of the sympathetic trunk, Johnson (1925) found no morphological differences by which he could clearly differentiate the former from the latter. His

studies, however, did not take into consideration the exact arrangement and distribution of the dendrites.

According to Müller, the myenteric plexus includes two types of neurons, viz.: neurons which lie quite free in the intermuscular spaces and neurons which sustain a peculiarly intimate relationship to the muscle. In sections of a flattened piece of intestine taken in the plane of the myenteric plexus, the cell bodies of the neurons of the former type usually appear rounded in outline and the dendrites which are relatively broad at the base and taper distally radiate in all directions. These dendrites may frequently be traced for some distance from the cell body. In some instances dendrites of neurons of this type terminate in foot-like enlargements in contact with the adjacent musculature. Not infrequently a single process, probably the axon, may be traced into the muscle. The neurons of the other type usually lie in close proximity to the musculature. The cell body is commonly elongated or pyriform and lies with its long axis parallel to the adjacent muscle. It usually gives rise to a relatively large cone-shaped process at the side toward the muscle. These processes, some of which give rise to terminal branches, terminate in small foot-like expansions in direct contact with muscle cells. Each neuron gives rise to one longer process which Müller regarded as the axon. Not infrequently one of these neurons may be observed in a slight depression in the muscle at the periphery of the ganglion. The neurons of this type, as Müller suggested, are of peculiar interest by reason of their intimate relationship, through their short dendrites, to the musculature. They are, however, less numerous than those of the other type. Müller emphasized the relatively large number of dendrites arising from some of the neurons in the myenteric ganglia, and stated that a process can frequently be traced from one of these neurons into a fibrous ramus which runs from the ganglion in question to a neighboring ganglion.

According to Hill (1927), the neurons in the myenteric ganglia in general conform to Dogiel's Types I and II. Those of Type I are characterized by short dendrites and those of Type II by longer dendrites. According to her observations, the neurons of Type I are easily recognizable in silver preparations, both by reason of their intense staining reaction and their superficial position in the ganglia. Their short dendrites not uncommonly form brush-like arborizations on the neurons located deeper and more centrally in the ganglia. More rarely the longer dendrites of the neurons of Type I ramify around the cell bodies of the more centrally located neurons or mingle with the fibers in the intercellular plexus. The axons of these neurons, according to Hill, can in some instances be traced for a considerable distance through neighboring ganglia and fiber tracts, but generally disappear among the fibers of the inter-

cellular plexus. She was never able to trace axons of neurons of Type I into the musculature nor outside the myenteric plexus; consequently, she did not regard these neurons as motor in function, but suggested that they may be associative.

The neurons of Type II, according to Hill, are larger and more variable than those of Type I. Although the majority of them are multipolar, she regarded the bipolar and unipolar neurons observed in her preparations as belonging to this type. The dendrites of these neurons are relatively long and branch freely. They commonly extend into a fiber bundle related to the ganglion of origin, and can frequently be traced for a relatively long distance. She was able to distinguish between dendrites and axon of neurons of this type only by their terminations. The dendrites commonly terminate in neighboring ganglia, where they form delicate plexuses, the fibers of which either terminate on the surfaces of ganglion cell bodies in minute knob-like swellings, or in a more diffuse manner in the intercellular spaces. The axon eventually passes into the musculature, where it terminates in relation to muscle cells. On the basis of these findings, she regarded the neurons of this type as motor in function.

Van Esveld (1928) also described the neurons in the myenteric ganglia in the cat as conforming almost perfectly to the two types of ganglion cells described by Dogiel. In preparations of the intestine of the cat he also observed ganglion cells of the same types imbedded in the circular muscle either singly or in small groups. These occurred most commonly near the mesenteric attachment. He also described the interstitial cells of Cajal as forming a synctium in intimate relationship to the musculature, and supported the theory advanced by Cajal, that this structure is composed of true nervous tissue.

According to Müller, the neurons in the myenteric plexus in the stomach and intestine are not enclosed in pericellular capsules. My own (1922) observations corroborate this finding, at least for the small intestine. Hill (1927) also was unable to observe pericellular capsules in the enteric ganglia. According to Greving (1920), the neurons in the myenteric plexus in the esophagus are enclosed in pericellular capsules. In the stomach and intestine, according to his findings, numerous cells with small rounded nuclei, and no apparent processes, lie scattered between the neurons throughout the ganglia, but do not form pericellular capsules. Cells of the same kind also occur in the fiber bundles connecting the myenteric ganglia. Müller found the ganglia more numerous, but smaller, in the myenteric plexus in the stomach and large intestine than in the small intestine. The myenteric plexus in the rectum is especially rich in ganglion cells.

In the submucous plexus in the intestine the neurons are, in

general, smaller and more compactly aggregated in the ganglia than in the myenteric plexus. They are also less angular in outline, except in instances in which, as observed by Müller, they seem to be pressed together in the ganglionic mass. The dendrites of these neurons are relatively long and may frequently be traced beyond the borders of the ganglion into the fibrous rami. As was pointed out by Müller, it is in most instances quite impossible to distinguish between axon and dendrites in this plexus. My own (1922) observations regarding the character of the neurons in the submucous plexus and the arrangement and distribution of their dendrites in the nerve fiber bundles connecting the ganglia, in general, corroborate those of Müller. According to Hill (1927), the submucous plexus includes only neurons of Dogiel's Type II. The fact that many of the neurons in the submucous plexus send their dendrites far beyond the confines of the ganglion in which the cell body is located, as will be pointed out below, has an important bearing on the interpretation of the functional relationships of these neurons.

Ganglion cells are present in great abundance in the submucous plexus throughout the small intestine, but in still greater abundance, according to Müller, in the large intestine, particularly in the rectum. Data regarding their frequency in the stomach are relatively meager. It may be assumed, however, that they are also present in considerable abundance in the submucous plexus in this division of the digestive tube. As stated above, certain investigators have described ganglion cells in the submucous plexus in the esophagus while others failed to find any nerve cells in the submucosa in this division of the digestive tube. It may be stated in this connection that, according to the experience of all investigators in this field, it is more difficult to obtain satisfactory preparations for the study of the neurons in the submucous than in the myenteric plexus. Not infrequently, preparations in which the neurons in the myenteric plexus are stained satisfactorily either fail to reveal the neurons in the submucous plexus or show them so poorly stained that their frequency and the details of their structure cannot be determined. These technical difficulties seem to be even greater in the esophagus and stomach than in the intestine.

Pericellular capsules have not been described in the ganglia of the submucous plexus, but small cells with rounded nuclei, like those described above as lying between the neurons in the ganglia of the myenteric plexus, are present also in the ganglia in the submucous plexus.

The Intercellular Plexus.—In the ganglia of both the myenteric and submucous plexuses there exists an intraganglionic fiber complex which is made up in part of the processes of the local neurons and in part of fibers of extrinsic origin. This fiber complex is, in general, more abundant in the myenteric than in the submucous ganglia.

In the ganglia of either plexus the fibers of extrinsic origin are mainly small unmyelinated fibers which stain darkly in pyridine silver preparations. Those of local origin include both large and small fibers. The large fibers represent mainly the short dendrites and the proximal portions of the longer dendrites. The distal portions of the longer dendrites, like the fibers of extrinsic origin, are slender and stain darkly in pyridine silver preparations. The large fibers usually run through the ganglion in various directions without showing much evidence of plexus formation. The smaller fibers commonly give rise to very fine intercellular plexuses.

In an effort to determine the sources of the fibers which give rise to the intercellular plexuses in the myenteric ganglia, Johnson (1925), using cats as the experimental animals, carried out three sets of experiments. In one group of animals all the nerves entering the intestinal wall by way of the mesentery and mesenteric vessels were cut. In another group, the splanchnic nerves were divided bilaterally just before they enter the celiac plexus. In a third group, the vagi were cut just below the diaphragm. After allowing time for the degeneration of the cut fibers, the myenteric plexus was studied in pyridine silver preparations of the intestine. According to Johnson's findings, section of all the extrinsic nerves to the intestine resulted in complete disappearance of the intercellular plexuses in the myenteric ganglia. The fibers which remained are clearly the processes of local ganglion cells. These fibers, according to Johnson, divide repeatedly and terminate in the adjacent smooth muscle. Section of the splanchnic nerves resulted in no apparent change in the myenteric plexus. He concluded, therefore, that the splanchnic fibers do not enter into the pericellular plexus in the myenteric ganglia. Section of the vagi in the two animals which survived, resulted in "apparently complete degeneration of the fine intercellular plexus." In these cases, there still remained, in addition to the processes of the local ganglion cells, a considerable number of small unmyelinated fibers which Johnson regarded as postganglionic sympathetic fibers.

The results of these experiments seem to indicate that the pericellular plexuses in the myenteric ganglia, which are brought out so well in pyridine silver preparations, are made up of the terminal portions of preganglionic vagus fibers. They also indicate that the postganglionic sympathetic fibers which enter the intestinal wall pass through the myenteric plexus, but apparently take no part in the formation of the intercellular plexuses. If, as seems highly probable, the synapses of preganglionic with enteric neurons are affected through the intercellular plexuses, these findings conform fully to the current teaching, according to which, the efferent vagus fibers supplied to the intestine are preganglionic and enter into synaptic relationship with neurons in the enteric plexuses, while the

sympathetic fibers which enter the intestinal wall through the extrinsic nerves terminate in direct relationship to the musculature without making synaptic connections with enteric neurons.

According to the above interpretation, vagus and sympathetic fibers sustain the same relationships to the enteric plexuses as to other peripheral plexuses, *e. g.*, the pulmonary and cardiac plexuses. It does not follow, however, that all the neurons in the enteric plexuses are components of vagus efferent chains. The great abundance of these neurons has been emphasized by various investigators, and it has seemed to some quite impossible that the pre-ganglionic vagus fibers could effect synaptic connections with all of them. Langley (1922) attempted to obviate this anatomical difficulty by postulating intermediate mother cells of vagus origin. According to Langley's scheme, each vagus fiber is supposed to effect synaptic connections with a number of mother cells, each of which in turn effects synaptic connections with a number of other enteric neurons. Anatomical evidence for the existence of such intermediate neurons in the vagus efferent chains, however, is wanting.

Hill (1927) did not agree with Johnson regarding the composition of the intercellular plexuses in the myenteric ganglia. She maintained that they are made up in part of the terminal portions of preganglionic vagus fibers and in part of the processes of the enteric neurons. This is in full accord with the evidence presented by her in support of the contention that many of the dendrites of the enteric neurons terminate in relation to the cell bodies of neurons in neighboring ganglia or adjacent neurons in the same ganglion, and the conclusion that the axons of the neurons of Type I terminate within the myenteric plexus. More exact knowledge regarding the composition of the intercellular plexuses in the enteric ganglia awaits further investigation. The theory that the terminations of preganglionic vagus fibers on enteric neurons constitute the only neuron junctions in the enteric ganglia, however, is no longer tenable.

Anatomical Evidence for the Occurrence of Enteric Reflex Arcs.—

There is an ever-increasing volume of physiological data, the interpretation of which seems to require the existence of local reflex mechanisms in the enteric nervous system. This has stimulated the search for the anatomical components of such reflex mechanisms. The majority of the anatomical studies, however, have failed to produce any positive evidence for the occurrence of afferent enteric neurons. It has quite generally been assumed that in order to prove the afferent or sensory character of any of the enteric neurons it would be necessary to demonstrate the connection of their processes with the mucous epithelium or with definite sensory endings in the gastro-intestinal wall. The technical difficulties involved in this can be best appreciated by those who have undertaken a detailed study of the enteric plexuses.

Dogiel (1896) was able to trace fibers, which he regarded as dendrites, from neurons in the myenteric plexus to the gastrointestinal mucosa. Smirnow (1893) had previously reported that he was able to trace nerve fibers into the digestive epithelium. R. Müller

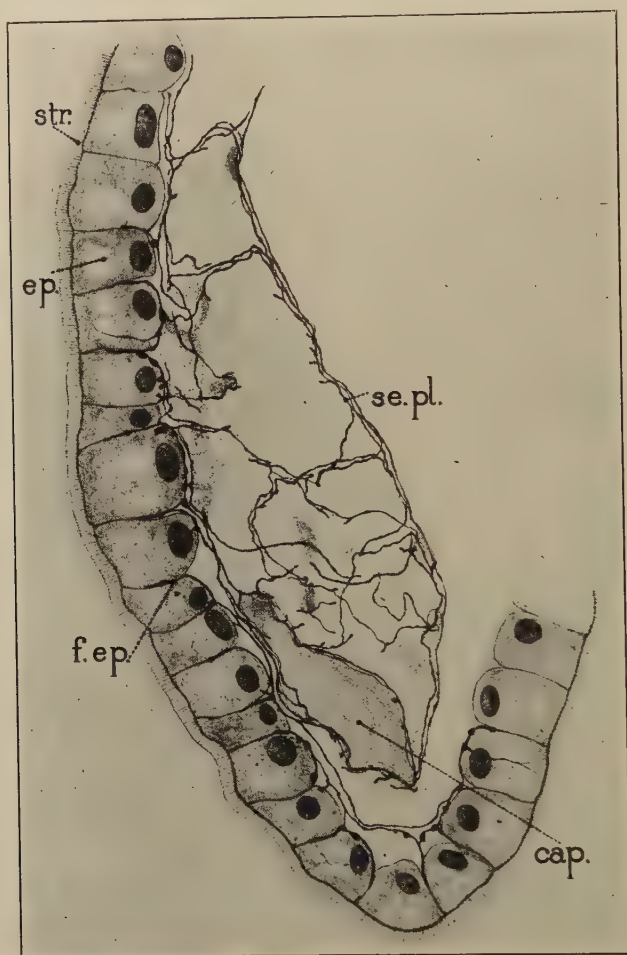


FIG. 43.—Subepithelial plexus and nerve terminations between the epithelial cells of a villus in the small intestine of a new-born rabbit (silver method of de Castro). (Catherine J. Hill.) *Cap.*, capillary; *ep.*, epithelial cell; *f.ep.*, terminal branch of a nerve fiber between epithelial cells; *se.pl.*, subepithelial plexus.

(1908) also reported that he was able to trace nerve fibers to the gastric epithelium in the frog, where they divided repeatedly. He also observed that some of the terminal branches penetrated the epithelium between the tapering basal ends of the epithelial cells.

Sakusseff (1897) claimed to have traced nerve fibers from the enteric plexuses to the mucous epithelium in the intestine of fishes. According to his description, the terminal branches of these fibers ramify beneath the epithelium and send varicose filaments into it which run between the epithelial cells and finally terminate in a network about individual cells. These findings have not been corroborated by the results of the majority of the more recent studies and have, therefore, been regarded with skepticism, especially by anatomists.

In preparations of the intestine of the cat, we described structures which were interpreted as nerve fiber terminations in the intestinal



FIG. 44.—Subepithelial plexus and nerve terminations between the epithelial cells of a villus in the small intestine of the dog (pyridine silver). (Waddell.) *f.ep* terminal branch of a nerve fiber between epithelial cells; *Se.pl.*, subepithelial plexus

epithelium (Kuntz, 1922). In favorable methylene-blue preparations fibers could be traced from the submucous plexus through the muscularis mucosæ into the intestinal villi, where some of them were distributed to the muscle fibers which extend into the villi, while others approached the intestinal epithelium and terminated in simple arborizations among the epithelial cells. These findings have recently been corroborated by the work of Hill (1927), who described a relatively rich subepithelial plexus of nerve fibers in the intestinal villi in the cat and rabbit, from which fine fibrils penetrate the epithelium and terminate in relation to the epithelial cells (Fig. 43). Waddell (1928) observed a similar subepithelial plexus and fiber

terminations in the epithelium in pyridine silver preparations of the intestine of the dog (Fig. 44). Hill regarded these fibers as sensory in character, but of extrinsic origin, probably afferent vagus components. It is interesting to note in this connection that Müller (1911) pointed out that many of the neurons in the submucous plexus send dendrites as well as axons into the internodal rami. While he attached no functional significance to this fact, it suggested the possibility that some of these dendrites might extend to the mucous epithelium or terminations located elsewhere, through which afferent impulses are received. Such neurons would meet the requirements of afferent components of enteric reflex arcs.

If it could be demonstrated that two neurons, either in the same or separate enteric ganglia, sustain a synaptic relationship to each other, the neurons in question might be regarded as the components of a local reflex arc. The termination of a process of one enteric neuron on the cell body of another has been described (Kuntz, 1922). In methylene-blue preparations of the intestine of the cat, a process of a ganglion cell which showed an intense staining reaction could in some instances be traced without interruption to its termination in a pericellular network on the lightly stained cell body of another neuron in the same ganglion. Although these pericellular networks resemble very closely the intracapsular pericellular networks which have been described in other parts of the autonomic nervous system and interpreted as synapses, they might still be regarded as pericellular terminations of dendrites. In other instances, however, fibers which enter a ganglion in the myenteric plexus through a ramus which connects it with a ganglion in the submucous plexus could be traced to their terminations in similar pericellular networks on the cell bodies of lightly stained neurons.

Although the possibility that these fibers represent dendrites is not precluded, it seems more probable that they are the axons of neurons in the submucous plexus. If they are axons, the terminations in question must be regarded as synapses. Since the fibers apparently run from the submucous into the myenteric plexus, they cannot reasonably be interpreted as visceral efferents, but must be regarded as fibers of local origin. Both in the myenteric and the submucous plexus fibers could be traced from one ganglion without interruption to pericellular terminations of the same type in neighboring ganglia. Some of these, especially in the myenteric plexus, might possibly be interpreted as synapses of preganglionic vagus fibers with enteric neurons. The intercellular plexuses which, in Johnson's (1925) experiments, underwent degeneration following vagus section and were, therefore, regarded by him as effecting the synapses of the preganglionic vagus fibers with enteric neurons, however, are grosser structures and sustain a less intimate relationship to the cell bodies of the enteric neurons than the pericellular

terminations in question. It seems highly probable, therefore, that the latter represent synapses involving two enteric neurons.

According to the current teaching, two enteric neurons which sustain a synaptic relationship to each other cannot be regarded as terminal links of a vagus efferent chain. They must either be interpreted as components of a local reflex arc, even though the dendrites of the one cannot actually be traced to terminations of a recognized sensory type, or the existence of association neurons in the enteric plexuses, as suggested by Hill (1927), must be conceded. The former of these two possibilities seems to us the more probable on anatomical grounds. It is also supported by abundant physiological data which will be considered below.

The results of the work of Johnson (1925) cited above failed entirely to corroborate these findings. In his preparations of the intestine in which the intercellular plexuses were absent, following degeneration of the extrinsic nerves, he found no evidence of synapses in the myenteric ganglia. It may be stated in this connection that the pyridine silver technique is not adapted to bring out such delicate pericellular structures as those observed in methylene-blue preparations. Even in these preparations, pericellular terminations could be observed only on the cell bodies of neurons which were stained but lightly. Intracapsular pericellular terminations have been described in methylene-blue preparations of other sympathetic ganglia. We have not been able to find that such terminations have been observed in pyridine silver preparations in any part of the autonomic nervous system. Further investigation of the relationships of enteric neurons to each other and the exact sources of the nerve fibers which terminate in the gastro-intestinal epithelium, especially by the use of the methylene-blue technique, would be highly desirable.

The Enteric Nerve Net Theory.—There has long been a tendency on the part of certain investigators to regard the enteric nervous system as composed, at least in part, of nerve nets characterized by actual protoplasmic continuity between the constituent cellular elements. Bethe (1903) and R. Müller (1908) describe the enteric plexuses in the frog as consisting of true nerve nets. They were still unconvinced, however, of the validity of the neuron theory, and probably did not regard these plexuses as differing fundamentally from other parts of the sympathetic nervous system. Erick Müller (1920) described the enteric plexuses in the *Selachii* as consisting exclusively of syncytial nerve nets. In a later paper (1921), he described the enteric plexuses in birds and mammals as consisting in part of nerve nets and in part of neurons which do not anastomose with each other. He classified the ganglion cells in the enteric plexuses in birds and mammals as neurons of Types I and II of Dogiel, but did not agree with Dogiel, that neurons of

Type II also occur in the ganglia of the sympathetic trunks and prevertebral plexuses. Furthermore, he identified the interstitial cells of Cajal (1889), which were regarded by Dogiel (1895) and Huber (1913) as connective-tissue elements, with the neurons of Dogiel's Type II, and advanced the opinion that the neurons of Type I are of vagus, and those of Type II of sympathetic origin, *i. e.*, the cells which become differentiated into neurons of Type I are displaced into the walls of the digestive tube along the paths of the vagi, while those which become differentiated into neurons of Type II are displaced from the sources of the cells which give rise to the ganglia of the sympathetic trunks. Consequently, he assumed that the neurons of Type I remain functionally associated with the vagus and those of Type II with the sympathetic nerves, the former subserving a motor and the latter an inhibitory function. According to Müller, both the myenteric and the submucous plexus include free neurons and nerve nets. He also maintained that the myenteric plexus includes only neurons of vagus origin in the stomach, and neurons of both vagus and sympathetic origin in the intestine, while the submucous plexus includes only sympathetic neurons in both the stomach and intestine. He further assumed that conduction in the walls of the digestive tube is mediated by the nerve nets, and that local reflexes are to be interpreted as axon reflexes.

On the basis of his physiological findings, Bickel (1925) also supported the theory that the enteric plexuses include nerve nets as well as free neurons and that they include both cells of vagus and sympathetic origin. According to Bickel, the myenteric plexus contains only vagus (parasympathetic) elements in the stomach, and both vagus and sympathetic elements in approximately equal numbers in the intestine, while the submucous plexus contains both vagus and sympathetic elements in the stomach, and mainly sympathetic elements in the intestine.

The theory that the enteric plexuses in the stomach include neurons of both vagus and sympathetic origin is not supported by the results of some of the more recent investigations bearing on this point. The embryological studies of Abel (1919), Stewart (1920), Kuntz (1920-1925), and Uchida (1927), as set forth in Chapter V, show clearly that the cells which give rise to the enteric neurons in the stomach are displaced from the region of the hind-brain along the vagi. According to these studies, a contribution of cells to the enteric plexuses in the stomach from the primordia of the sympathetic trunks seems highly improbable. Neither L. R. Müller (1911), Kuntz (1922), Johnson (1925), nor Hill (1927) found any evidence for the existence of nerve nets in the enteric nervous system. Obviously, negative findings alone cannot disprove the existence of nerve nets. Johnson has pointed out very clearly that all the anatomical evidence available indicates contiguity rather than con-

tinuity of the nervous elements in the myenteric plexus in mammals. He also pointed out clearly that there are syncytial networks composed of connective-tissue elements in the intermuscular and sub-mucous layers in the intestine which may have been misinterpreted as nerve nets. These elements probably are identical with the interstitial cells described by Cajal and regarded by him as nerve cells. In spite of the evidence to the contrary advanced more recently, van Esveld (1928) again supported the theory that they are true nerve cells.

Anastomosing nerve cells were described by Cole (1925) in the myenteric plexus in the frog. In methylene-blue preparations these cells appeared to be connected by broad protoplasmic bands. They occurred in groups of two, three, or four cells and were found in both the ileum and rectum. The nervous nature of these cells seems to be established by the presence of chromidial substance. Furthermore, in most instances, an axon could be demonstrated for each cell of a given group. Cole regarded these anastomosing ganglion cells as belonging to the same category as binuclear ganglion cells, which are not uncommon in the autonomic ganglia in certain animals (Apolant, 1896; Carpenter and Conel, 1914). He also pointed out that there is a marked difference between these anastomosing ganglion cells and those found in the typical invertebrate nerve net. In the latter, axons and dendrites cannot be differentiated, but the cell processes are all alike. In the anastomosing ganglion cell groups described by Cole, only the dendrites were involved in the intercellular connections.

In pyridine silver preparations of the small intestine of the dog, Waddell (1928), working under my supervision, occasionally observed two ganglion cells in the myenteric plexus joined together by a single fiber. In some instances, the two cells joined together in this manner lay in proximity to each other; in others they were removed from each other by a distance equal to several times the diameter of a ganglion cell body. His preparations also exhibit ganglion cells joined together in pairs by relatively broad protoplasmic bands. Doubtless, the latter cells, like the anastomosing ganglion cells described by Cole in the intestine of the frog, belong to the same category as binuclear ganglion cells. We cannot, however, regard the ganglion cells joined together by a single well-differentiated fiber as belonging to the same category. Nor do we regard these findings as supporting the theory that the enteric plexuses in mammals are made up even in part of true nerve nets.

Nerve Fiber Terminations.—The majority of the nerve fiber terminations observed in the gastro-intestinal musculature conform to the mode which is typical for postganglionic autonomic fibers and may be regarded as efferent in character. The fibers supplying the gastro-intestinal musculature, in general, run parallel to the

muscle fibers, forming intramuscular plexuses, and eventually terminate in relation to the muscle cells. Hill (1927) described individual

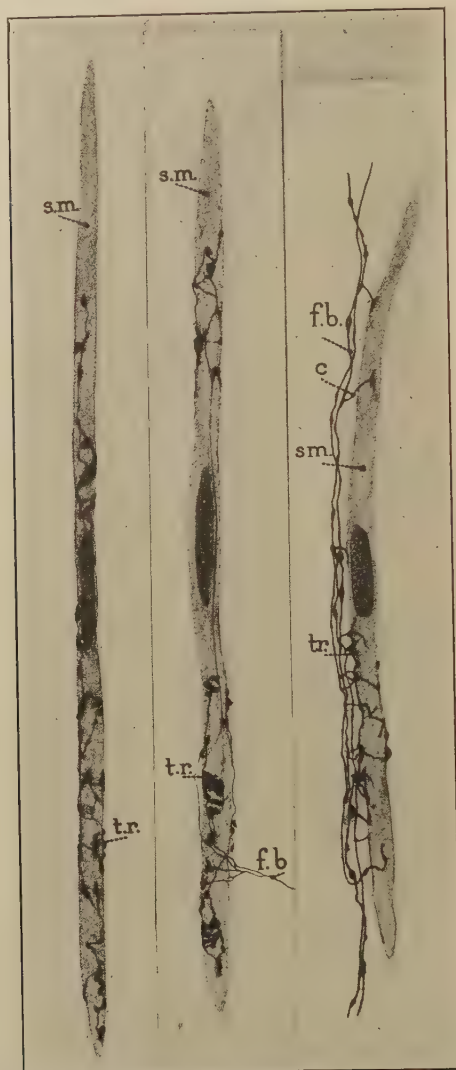


FIG. 45.—Endings of nerve fibers on smooth-muscle cells in the circular muscle layer in the small intestine of the rabbit (methylene blue). (Catherine J. Hill.) *fb.*, fibers giving rise to endings; *tr.*, terminal ramifications; *c*, collaterals.

fibers which “break up, on the surface of a muscle cell, into a number of fine fibrils which are beset with small varicosities and

which anastomose together to form a delicate network closely encircling its entire surface" (Fig. 45). Her observations led her to conclude that "the varicose swellings of the fibrils lie on the surfaces of the muscle cells and that extremely delicate fibrillæ take origin from these swellings and actually penetrate into the substance of the muscle fibers." Her observations regarding the efferent fiber terminations in the gastro-intestinal musculature, in general, corroborate those of Boeke (1926).

Afferent nerve fiber terminations have also been described in the gastro-intestinal musculature. Nemiloff (1902) described nerve fiber terminations which seem to be of a sensory type in the musculature of the large intestine of the frog. Similar terminations were observed by Cole (1925) in the circular muscle layer in the cloaca of the frog. Cole described these terminations as complex arborizations made up of the terminal unmyelinated branches of myelinated fibers. In methylene-blue preparations these terminal filaments are usually lightly stained and bear relatively large varicosities which often stain heavily. These probably are the terminations of general visceral afferent fibers. Carpenter (1918) described nerve fiber terminations, probably of a sensory type, in the stomach of the cat and the small intestine of the dog. Those observed in the stomach were described as terminal skeins and nets composed of fine varicose fibrils. They were found mainly in the longitudinal muscle in the cardiac region, but a few were also present in the serosa. They were connected with varicose, unmyelinated fibers, the source of which could not be determined. Those observed in the small intestine were described as tufts of exceedingly delicate varicose fibrils. They were present in both the longitudinal muscle of the small intestine and the subperitoneal connective tissue. These terminations were also connected with delicate varicose unmyelinated nerve fibers which could be traced centrally into the myenteric plexus, but whose exact source could not be determined. They probably represent the terminal branches of visceral afferent fibers. These terminations, as Carpenter also pointed out, are so situated that they could be stimulated directly by contraction or distention of the musculature in which the majority of them are located.

That general visceral afferent fibers, especially of vagus origin, terminate in the esophageal mucosa is well known, although their terminations have not been described adequately. As stated above, fiber terminations which must be regarded as sensory in character also occur in the gastro-intestinal epithelium. Some of the latter probably are general visceral afferent components, but since nerve fiber terminations exist in this epithelium in considerable abundance it seems highly probable that some of the fibers involved arise in the enteric ganglia and represent local afferent fibers.

PHYSIOLOGY OF THE NERVES OF THE DIGESTIVE TUBE.

Esophagus.—The esophagus differs structurally from the other divisions of the digestive tube in that its musculature is made up of both striated and smooth muscle fibers. In a recent physiological study of the esophageal musculature in various animals (cat, dog, rabbit, guinea-pig, rat), Inoaka (1924) pointed out that kymographic records of induced muscle twitches, obtained from the lower thoracic portion of the esophagus in the cat and in part also in the dog, indicate various stages of transition from striated to smooth muscle. The records obtained from this portion of the esophagus in the other animals studied are essentially like those obtained from striated muscle. These results are in accord with the findings of von Brücke and his associates (1912, 1913) regarding action currents. In addition to the curves which are typical for striated muscle, they could also determine a slow phase which is characteristic of smooth muscle. The musculature of the esophagus in the dog seems to consist almost entirely of striated muscle. In the cat and the ape it consists mainly of striated muscle, but contains smooth muscle in larger proportion than in the dog. In man, the transition from striated to smooth muscle occurs in the upper thoracic portion of the esophagus, beginning somewhat higher in the anterior than in the posterior wall.

The chief function of the esophagus is illustrated by the swallowing reaction, by means of which food taken into the mouth is conveyed to the stomach. This reaction, which may be initiated as a voluntary act, becomes, during its execution, the swallowing reflex. The swallowing reaction may also be elicited as a pure reflex by stimulation of certain areas of the mucosa of the mouth and pharynx. These areas vary somewhat in different animals, but the afferent impulses involved are conveyed by fibers of the trigeminal, glossopharyngeal, or vagus nerves. The superior laryngeal branch of the vagus probably is involved most commonly in such afferent conduction. The glossopharyngeal also conveys impulses which inhibit the swallowing reflex. The efferent impulses involved in the swallowing reaction are mediated mainly through the glossopharyngeal and branches of the vagus nerves. The motor innervation of the esophagus involves the recurrent and certain thoracic branches of the vagus, the sympathetic supply, and the intrinsic plexuses. To what extent the sympathetic nerves play a part in the swallowing reflex is not definitely known. According to Inoaka (1924), the effective innervation of the esophagus in the dog is purely parasympathetic. He could elicit no apparent reaction by stimulation of the extrinsic sympathetic nerves. Neither has an antagonistic action of the vagus and sympathetic innervation of the esophagus been demonstrated in any animal.

Efferent stimulation of a single vagus branch to the esophagus

elicits a purely segmental contraction. A peristaltic wave which is propagated along the esophagus cannot be initiated by efferent stimulation of the esophagus at any given point. The esophagus differs in this respect from the lower divisions of the digestive tube. Stimulation of the central end of the divided vagus, while the other vagus is intact, results in contraction along the entire esophagus. This in turn stimulates the afferent vagus endings throughout the esophagus, thus sending up afferent impulses which activate the efferent neurons of the intact vagus, and result in still further contraction of the entire esophageal musculature.

That peristalsis in the esophagus, like the swallowing reflex, is mediated through extrinsic nerves was demonstrated by Mosso as early as 1876. He was able to show that transection of the esophagus or even resection of entire segments does not prevent peristalsis, if only the nerve supply to the several pieces remain intact. Meltzer (1906) also observed the propagation of peristaltic waves along the esophagus in the rabbit following its transection at several levels. He noted, however, that when the animal was under deep anesthesia, a peristaltic wave initiated in one segment stopped at the lower border of that segment and did not pass on to the next. A foreign body introduced into the esophagus results in a peristaltic wave beginning above the point of stimulation; consequently, if the primary reflex initiated at the beginning of the swallowing act succeeds only in forcing a bolus of food into the upper part of the esophagus, the bolus itself causes a series of reflex contractions by local stimulation of the sensory fibers, which tend to move the bolus downward. This, however, does not occur following section of the vagus supply, again showing that the peristaltic reflex is mediated through extrinsic nerves.

The orderly sequence of the movements involved in the swallowing reflex and esophageal peristalsis early suggested that these movements are regulated through a center in the medulla oblongata (deglutition center). This center is located lateral to the *ala cinerea* and just above it, and probably involves a portion of the *tractus solitarius* and *nucleus ambiguus*. Whether it consists of a definite group of cells which send their axons directly to the motor nuclei of the several efferent nerves concerned is not definitely known. The close coördination of the swallowing reflex and respiratory movements suggests that the deglutition center is intimately associated with the respiratory center. Respiration is always inhibited during deglutition.

That the swallowing reaction and esophageal peristalsis are also affected by psychic influences is well known. Strong emotional disturbances, *e. g.*, joy, anger, or fright, are not uncommonly accompanied by spasm of the pharynx and esophagus which may temporarily render the swallowing reaction impossible. Again, hysterical

individuals not infrequently complain of sensory disturbances in the esophagus which are, doubtless, associated with disturbances in its motor activity.

As stated above, it has not been demonstrated that the intrinsic neurons play any part in the swallowing reflex or esophageal peristalsis. Rhythmic contractions of isolated pieces of the esophagus have been observed, but this does not prove independent functional activity on the part of the intrinsic nerves. Section of the vagus fibers which supply the lower portion of the esophagus and the cardia results in spastic contraction of these parts. This condition subsides after a few days, and the parts involved resume functional activity, which continues in an apparently normal manner. This suggests that tonus and single contractions, at least in the lower portion of the esophagus, are influenced by the intrinsic nervous mechanism, although it has not been demonstrated that any single reaction involving the esophageal musculature is mediated solely through its intrinsic nerves.

Cardiac Sphincter.—The circular muscle is somewhat thickened at the cardiac orifice of the stomach and acts as a sphincter. The innervation of this sphincter includes both vagus and sympathetic fibers and the intrinsic nervous mechanism, particularly the myenteric plexus. The sympathetic fibers involved are derived mainly from the coeliac plexus, the corresponding preganglionic fibers are components of the greater splanchnic nerve.

The results of experiments involving stimulation of the vagus and sympathetic fibers to the cardiac sphincter are not all in full accord, by reason of differences in the innervation of this muscle in the various experimental animals and other variable factors. The interpretation of these results is beset by still further difficulties by reason of the fact that the fibers supplying the sphincter cannot be stimulated alone, *i. e.*, stimulation of these fibers is accompanied by stimulation of vasomotor and secretory fibers, and perhaps also by stimulation of the adrenals. Furthermore, the stage of anesthesia plays an important rôle. All these factors complicate the result of the experiment and cannot be disregarded.

The vagus, like the sympathetic supply to the cardiac sphincter, includes both motor and inhibitory fibers. If the muscle is relaxed or in a state of low tonus, vagus stimulation results in contraction; if the sphincter is closed, it results in relaxation, thus opening the cardiac orifice (Carlson, 1922). In Carlson's experiments, splanchnic stimulation resulted only in motor action of the cardiac sphincter in the dog, only in inhibitory action in the rabbit, and in both motor and inhibitory action in the cat. That relaxation of the cardiac sphincter is not the result of mechanical pressure, due to contraction of the esophagus which tends to force the esophageal content into the stomach, was clearly shown by Langley (1899),

who demonstrated, by the use of a water manometer, that following vagus stimulation liquids flow from the esophagus into the stomach under pressure conditions which are inadequate to bring about mechanical opening of the cardiac orifice. The peristaltic wave passing along the esophagus is preceded, at least in the lower part of the esophagus, by a wave of inhibition or relaxation which also affects the cardiac sphincter and the adjacent gastric musculature. In this manner the way is opened for the bolus, so that the peristaltic contraction may force it through the cardiac orifice without much resistance. By the use of the esophagoscope, Mikulicz (1903) was able to show that the cardiac sphincter remained closed until the tube of the instrument approached to within a few centimeters of the cardia, but as the tube approached more closely the sphincter gradually opened. Apparently, this reflex inhibition was elicited by stimulation of afferent fibers in the mucosa of the lower portion of the esophagus. Schilf (1926) maintained that the reflexes involved in this reaction pass through the central nervous system, and that both the afferent and efferent neurons involved are components of the vagus.

Following the passage of a bolus of food into the stomach, the cardiac sphincter again closes until another peristaltic wave passing down the esophagus approaches. According to Cannon (1911), the tonic contraction of the cardiac sphincter, which develops when the stomach contains food, is maintained through reflex activity of the intrinsic plexus initiated by the stimulating effect of the acid in the gastric secretion. Carlson (1922) also pointed out that the tonus of the cardiac sphincter is high while gastric digestion is in progress. According to his findings, however, "this hypertonus persists after removing the food from the stomach, washing the stomach cavity with water at body temperature, or rendering the stomach content alkaline; 0.4 per cent HCl in the stomach does not increase the tonus of the cardia parallel to that found in the digesting stomach." Carlson also observed that the tonus of the cardiac sphincter is diminished under light, but increased under deep anesthesia.

Stomach.—Although the musculature of the stomach is composed exclusively of smooth muscle fibers, it is more complex than that of the other divisions of the digestive tube. Its motor activities also are correspondingly complex. Furthermore, the gastric musculature, under the influence of the intrinsic nervous mechanism, possesses the capacity to undergo reflex adjustment to the changing volume of the gastric content without exhibiting appreciable changes in tonus (Cannon, 1911). According to Bruns (1920), the pressure within the stomach is not increased by an increase in the volume of the stomach content, nor does an increase in the volume of the stomach increase the intra-abdominal pressure, but the abdominal muscles undergo reflex adjustment to changes in

the gastric content. This latter reaction is a reflex phenomenon mediated through reflex arcs whose afferent limbs are components of the splanchnic nerves, and whose efferent limbs are components of the spinal nerves through which the abdominal muscles are supplied.

That gastric motility is not interrupted following bilateral section of vagus and splanchnic nerves is well known. Indeed, activity may still be observed, under proper conditions, in the excised stomach. As far as its motor activities are concerned, therefore, the stomach may be regarded as an automatic organ. Its automatic activities are elicited by stimuli which arise within itself, and seem to be carried out through its intrinsic nervous mechanism. These activities, however, are normally regulated and controlled through the vagus and splanchnic nerves.

In general, vagus stimulation augments gastric peristalsis. Very strong vagus stimulation commonly results in a very marked increase in the tonus of the gastric musculature, especially in the region of the pars media and the pyloric antrum. Indeed, tonus may be increased to such an extent in these parts that the peristaltic waves are no longer apparent, and a condition of pylorospasm may exist (Böwing, 1924). On the other hand, vagus stimulation may result in inhibition of gastric motility. Langley observed this as early as 1898 and concluded that the vagus supply to the stomach also includes fibers whose action on the gastric musculature is inhibitory. Carlson (1922) also observed that the vagus contains fibers which inhibit the gastric musculature. It is highly probable, as was suggested by Schilf (1926), that the various experimental animals differ with respect to the occurrence and frequency of fibers in the vagus nerve which exert an inhibitory influence on the gastric musculature.

Splanchnic stimulation commonly results in inhibition of gastric peristalsis and relaxation of the gastric musculature, but certain investigators (Morat, 1893; Dixon, 1902) observed an opposite effect. Openchowski (1899) maintained that the splanchnic nerves include both motor and inhibitory fibers. On the basis of effects produced by adrenalin, Smith (1918) concluded that the splanchnic nerves are purely inhibitory in man and the cat, but inhibitory only for certain regions of the stomach and motor for others in the guinea-pig, rabbit, and dog. According to Carlson (1922), the splanchnic nerves carry both motor and inhibitory fibers to the stomach.

Pyloric Sphincter.—According to most observers, the pyloric sphincter responds to both vagus and splanchnic stimulation in essentially the same manner as the gastric musculature. Certain investigators, especially Smith (1918), Klee (1919), and Koennecke (1922), have pointed out, however, that splanchnic stimulation not uncommonly results in contraction of the muscle. According to Thomas and Wheelon (1922), the effect of stimulation of the extrinsic

nerves is the same on the motility of the pyloric sphincter as on that of the pyloric antrum. This finding supports the theory that the pyloric sphincter is not a separate functional entity, but that the pyloric antrum and sphincter constitute a functional unit and have a common nerve supply. According to the results of their experiments, the function of both the vagus and splanchnic fibers supplying the pyloric sphincter is mainly motor. Both nerves also contain fibers which are inhibitory to the pyloric sphincter, but these are more abundant in the splanchnic than in the vagus. They also called attention to the fact that the nerve supply to the stomach and pyloric sphincter cannot be clearly differentiated into functionally distinct sympathetic and parasympathetic divisions.

The effects of artificial stimulation of the extrinsic nerves in question indicate the functional character of their efferent fibers, but afford no adequate conception of the normal functioning of the pylorus. When food is taken into the stomach, contractions are initiated about the middle of the organ and advance toward the pylorus. As digestion progresses, these contractions become stronger and, at certain irregular intervals, but not with each contraction wave, the pylorus opens as a wave of contraction approaches. Klee (1912), who, by the use of the fluoroscope, observed the movements of the stomach elicited by vagus stimulation while it contained a barium meal, carefully described these movements. According to his observations, the pyloric sphincter relaxes quite suddenly shortly before a wave of contraction reaches the pylorus, allowing the entire food mass, which was separated from the rest of the stomach content by the contraction in question, to pass into the duodenum, but he never observed opening of the pylorus unless the approaching wave of contraction carried a mass of the stomach content before it. It appears, therefore, that the relaxation of the pyloric sphincter was not the direct result of vagus stimulation, but the result of the peristaltic contraction which carried a mass of the stomach content into the pyloric region. Whether chemical stimuli played a rôle in the reflexes involved in this process could not be determined. It was further observed that when a considerable mass of the stomach content had passed into the duodenum and still remained there, the pylorus did not open at the approach of a peristaltic wave of contraction which carried an adequate volume of the stomach content before it, regardless of the strength of the peristaltic contraction. The normal functioning of the pyloric sphincter seems to be controlled by closely coördinated reflex mechanisms which involve both the stomach and duodenum.

The Nervous Mechanism of Vomiting.—Vomiting is a reflex reaction which borders on the pathological, and not infrequently serves the useful purpose of ridding the stomach of harmful substances. The rôle of the stomach in this reaction consists in tonic

contraction of the pylorus and pyloric antrum, inhibition of fundic peristalsis, and relaxation of the cardia and cardiac sphincter. The gastric content is expelled through the esophagus by the sudden and simultaneous contraction of the diaphragm and abdominal muscles (Cannon, 1911). Vomiting is commonly caused by abnormal stimulation of the terminations of afferent vagus fibers in the stomach. It may also be elicited by artificial stimulation of afferent vagus fibers and other sensory nerves. Not infrequently it is caused by disturbances of the urogenital apparatus, liver, and other visceral organs. It may also be caused by disagreeable emotions and disturbances of equilibrium. The efferent impulses involved reach the medulla regardless of whether they are conveyed by the vagus or other afferent nerves. The efferent impulses through which contraction of the pyloric sphincter and antrum is brought about are mediated by the vagus; those which bring about inhibition of the fundus and relaxation of the cardia are mediated by the splanchnic nerves. The contraction of the diaphragm and abdominal muscles is brought about by impulses mediated by the phrenic and lower thoracic nerves. Whether there is a special group of cells in the medulla which constitutes the vomiting center is not definitely known. The coördinated impulses which are sent out to the various muscles involved arise in the medulla, probably in the region of the respiratory center.

Vomiting is not infrequently a symptom of disease or injury of the brain (meningitis, brain tumor, etc.) which brings about an increase in intracranial pressure. In this condition, the direct cause of vomiting probably is the increased hydrostatic pressure in the fourth ventricle which stimulates the vagus nuclei directly. Localized injuries of the brain and spinal cord are not commonly accompanied by vomiting.

Nervous Regulation of Gastric Secretion.—That gastric secretion is regulated in part by nervous influences has long been known, but knowledge of the specific effects of the various components of the gastric nerve supply on secretory activity has awaited the results of relatively recent investigations. Important contributions along these lines were made by Bickel and his associates. According to their findings, as set forth by Bickel (1925), the chief and parietal gland cells in the fundus are innervated by both parasympathetic and sympathetic fibers which excite and sympathetic fibers which inhibit secretory activity. The parasympathetic fibers exert the major influence in the secretion of water and hydrochloric acid in this part of the stomach, while the sympathetic secretory fibers play but a secondary rôle in this function. On the other hand, the sympathetic secretory fibers exert the major influence in the secretion of enzymes, while the parasympathetic fibers play but a secondary rôle in this function. The sympathetic inhibitory fibers

inhibit all secretory activity. The chief cells in the pyloric region are innervated only by sympathetic fibers, some of which excite and others inhibit secretion. In this part of the stomach, the sympathetic secretory fibers excite both the secretion of enzymes and water, but water is secreted by the pyloric glands only in relatively small quantities. According to Bickel, all nervous excitation and inhibition of gastric secretion is mediated through the extrinsic nerves.

According to de Vecchi (1927), who cited the experimental work of Foa, section of the sympathetic nerves in animals was followed by a marked increase, and section of branches of the vagi by a marked diminution in the quantity of hydrochloric acid secreted in the stomach. Section of both sympathetic and vagus branches was followed by slight diminution in the quantity of hydrochloric acid secreted. He also cited two clinical cases in which resection of the vagus branches along the lesser curvature of the stomach and the sympathetic nerves approaching the pyloric region was followed by diminution of hydrochloric acid secretion, which was still appreciable after one and a half years.

Under normal physiological conditions, the secretory activity of the fundic glands ceases while the stomach is empty. The pyloric glands, however, remain active, producing in small quantities an enzyme-containing secretion, in which the pepsin must remain inactive by reason of the lack of hydrochloric acid, unless hydrochloric acid is secreted in small quantities by the parietal cells. According to Aschoff (1923), parietal cells are regularly present in the glands in closest proximity to the pyloric sphincter. The inhibition of the fundic glands, according to Bickel, probably is due to inhibitory impulsés of central nervous origin conveyed by sympathetic fibers incorporated in the vagus nerve, which probably are absent in the pyloric region. When food is taken into the mouth, the stimulation of the sense organs involved and the accompanying psycho-physiological processes initiate strong reflex parasympathetic excitation, in the presence of which the central inhibitory influences, acting on the fundic glands, gradually subside, and these glands are thrown into secretory activity. As the food enters the stomach, it stimulates the gastric mucosa directly, first in the fundus, then in the pyloric region, and somewhat later in the duodenum, giving rise to afferent impulses which are conveyed by the general visceral afferents to the appropriate centers in the central nervous system. These, in turn, give rise to both secretory and inhibitory impulses which are conveyed back to the glands by general visceral efferent fibers. As the process of digestion progresses, the secretin produced by the active mucosa and the secretin-like substances contained in the food reach the intestine and, being absorbed, are added to the

secretin already present in the blood. This, in turn, exerts an influence on the secretory activity of the gastric glands.

As the food passes into the intestine, and the stomach once more becomes empty, both the reflex and humoral excitation of the gastric glands subsides and the central inhibitory impulses again gain the ascendancy, the fundic glands become quiescent and the pyloric glands, in the absence of reflex inhibition, continue their normal secretory activity.

Although nervous influences play an important rôle in gastric secretory activity, this rôle must be regarded as purely regulatory. Secretion is an inherent function of the gland cells and constitutes a manifestation of their metabolic activity. This activity is subject to a measure of regulatory control due to the effect of secretin in the blood and other non-nervous factors in their environment. Gastric secretion is not interrupted in the absence of nervous impulses, but continues subject only to the measure of control which is afforded by these non-nervous factors.

Intestine.—In general, vagus stimulation results in contraction of the intestinal musculature as far as the distribution of vagus fibers extends. In Boehm's (1913) experiments, vagus stimulation produced no effect in the large intestine of the dog and the rabbit, but elicited contraction in the proximal part of the large intestine in the cat. Stimulation of the sacral parasympathetic nerves commonly elicits contraction of the smooth muscle in the descending colon, rectum, and anal canal. Bayliss and Starling (1913) pointed out that contraction of the intestinal musculature elicited by vagus stimulation is preceded by inhibition in the dog. They concluded, therefore, that the vagus also contains fibers which inhibit the intestinal musculature. This conclusion has since been confirmed by other investigators also in other animals.

In general, stimulation of the splanchnic or hypogastric nerves elicits inhibition of the intestinal musculature. In some instances, however, this inhibition is preceded by contraction. It may be assumed, therefore, that these nerves also contain motor fibers to the intestine. Splanchnic stimulation commonly elicits contraction of the ileocolic sphincter. According to Magnus (1908), stimulation of either the vagus or pelvic nerves is without effect on this muscle.

The anal canal is guarded by an internal and an external sphincter muscle. The external sphincter ani is composed of striated muscle and is subject to voluntary control within certain limits. It is supplied by the inferior hemorrhoidal branch of the pudendal nerve. The internal sphincter ani is composed of smooth muscle. Like the rest of the smooth musculature of the anal canal, it is supplied by sympathetic and parasympathetic nerves. Both the internal and external sphincters are normally in tonus, but the force of the tonic contraction of the external is normally greater than that of

the internal sphincter. The effects on the internal sphincter and of artificial stimulation of its sympathetic and parasympathetic innervation seem to vary in different animals.

Normal defecation is in part a voluntary and in part an involuntary act. Under certain conditions defecation may be carried out as a pure reflex. The defecation reflex involves peristaltic contractions of the rectum or the entire colon, together with inhibition of the anal sphincters. This reflex is normally excited by the entrance of feces into the rectum (Cannon, 1911; Müller, 1911). According to Müller (1911), defecation may be inhibited voluntarily by contraction of the muscles of the pelvic floor. Contraction of these muscles gives rise to afferent impulses which bring about reflex inhibition of the movements of the colon and rectum.

Normal defecation usually involves reflexes through the spinal cord. Destruction of the lumbar and sacral portions of the spinal cord results in a temporary diarrhea lasting for several days. This is followed by normal evacuation of the large intestine at the usual intervals (Goltz, 1896). The results of destruction of the spinal cord vary somewhat in different animals (Elliott and Barclay-Smith, 1904), but, when freed from both motor and inhibitory control through the spinal cord, the local nervous mechanism seems to have the capacity to regulate and control the defecation reflex (Müller, 1911).

Reflexes mediated through the extrinsic nerves play only a minor rôle in the control of intestinal activity, yet reflex inhibition of the movements of the small intestine may be brought about by stimulation of any afferent nerve. The reflexes involved are mediated through centers in the medulla and spinal cord and are carried out through the splanchnic nerves (Hotz, 1909). According to Lehmann (1913), inhibition is the only effect on the small intestine which can be brought about by stimulation of afferent nerves. On the other hand, afferent stimulation of the vagus and somatic nerves exerts a motor influence on the large intestine, while afferent stimulation of splanchnic, hypogastric, and visceral sacral nerves exerts mainly an inhibitory influence on this division of the digestive tube. Lehmann further pointed out that reflexes affecting the intestine which are elicited by stimulation of the vagus and somatic afferent nerves, are, in general, mediated through centers in the medulla, while those elicited by afferent stimulation of the splanchnic, hypogastric, and visceral sacral nerves are mediated through centers in the spinal cord.

Physiological Evidence for the Occurrence of Enteric Reflex Mechanisms.—The data obtained from experiments involving artificial stimulation of the extrinsic nerves supplying the various divisions of the digestive tube at best afford only an inadequate basis for the interpretation of the nervous reactions involved in the

motility of the digestive tract. We have observed that both sympathetic and parasympathetic nerves may conduct both motor and inhibitory impulses to the gastro-intestinal musculature. This neither proves that the parasympathetic nerves normally contain sympathetic fibers nor that the sympathetic nerves normally contain parasympathetic fibers, but suggests that the motor and inhibitory functions cannot be sharply delimited by artificial stimulation, and that the results of such experiments can have only a limited physiological significance.

Following an extensive study of the changes in tonus and motor movements of the gastro-intestinal musculature brought about by the administration of various drugs and section of extrinsic nerves, Bickel (1925) advanced the hypothesis that every muscle cell, whether it be striated or smooth, must possess a fourfold innervation. As applied to smooth muscle this hypothesis implies that parasympathetic fibers which subserve tonus work in harmony with sympathetic fibers which subserve the same function, and that the antagonists of the fibers of both these types are inhibitory (tonus negative) sympathetic fibers. This hypothesis is highly suggestive, but can at present be regarded only as a hypothesis which lacks anatomical verification. Neither does it shed any additional light on the independent functioning of the enteric nervous system.

Section of extrinsic nerves, as pointed out above, does not interrupt gastro-intestinal motility. Neither does it profoundly modify the gastro-intestinal movements. Furthermore, there is a strong tendency on the part of the system to restore normal functional activity in a relatively short time following the disturbances which arise as the result of such operative interference. For example, bilateral vagus section at the level of the diaphragm results in diminution of tonus of the gastro-intestinal musculature and retardation of peristalsis, but both tonus and peristaltic activity are soon restored to the condition which existed before vagotomy. Bilateral section of the splanchnic nerves results in increased tonus and augmented peristaltic activity. This also subsides in a relatively short time and is followed, in some instances, by a hypotonic condition. Section of both vagus and splanchnic nerves results in marked hypotonicity of the stomach and retardation of peristalsis. This condition is of longer duration following bilateral than following unilateral section of these nerves (Bickel, 1925). Section of the sympathetic nerves supplying the large intestine not uncommonly results in mild diarrhea which gradually subsides. In our experimental animals (cats and dogs), frequent discharge of soft feces was observed, in many instances, for some time following removal of the inferior mesenteric ganglia or extirpation of the lumbar sympathetic trunks. Relief of chronic constipation in man has also been reported following lumbar sympathectomy.

Obviously, the nervous phenomena involved in the normal functioning of the digestive tube cannot be adequately explained on the basis of motor and inhibitory control mediated through the sympathetic and parasympathetic outflows from the central nervous system; many reactions must involve only the enteric nervous system. In view of this fact and the anatomical structure of the enteric plexuses, it seems desirable to undertake a critical analysis of some of the physiological data which seem to indicate that the enteric nervous mechanism is a reflex system capable of functioning quite independently of central nervous control.

Gastro-intestinal motility of all known types has been observed following section of the extrinsic nerves supplying the part of the digestive tube in question. It may be assumed, therefore, that this motility, though normally subject to central nervous influences through the extrinsic nerves, originates in the neuromuscular mechanism in the wall of the gastro-intestinal canal. Gastro-intestinal motility of certain types probably is myogenic. Whether gastro-intestinal motility of certain other types is initiated in the enteric nervous system or in the enteric musculature must at present be regarded as an open question. Certain reactions which are commonly recognized as reflexes are quite certainly initiated in the enteric nervous system and carried out through it.

Enteric Reflexes.—As observed by Cannon (1906), the differences in the rate of discharge of different kinds of food from the stomach persist following bilateral section of both splanchnic and vagus nerves. Relaxation of the pyloric sphincter when the content of the pyloric antrum becomes acid occurs also in the excised stomach (Cannon, 1907). According to Brunemeier and Carlson (1915), mechanical and chemical stimulation of the upper part of the intestinal mucosa inhibits gastric tonus and hunger contractions. These reactions persist, but are less marked following bilateral section of both vagus and splanchnic nerves. It may be assumed, therefore, that these and similar responses elicited by stimulation of the gastric mucosa involve local as well as cerebrospinal reflex mechanisms. Mechanical irritation of the duodenal mucosa through a duodenal fistula in dogs with extrinsic nerves to the stomach and intestine intact, as observed by Luckhardt, Phillips, and Carlson (1919), elicits tonic contraction of the pyloric sphincter. The same phenomenon was observed by Thomas and Kuntz (1926) in dogs which had been subjected to bilateral section of both vagus and splanchnic nerves. This reaction could not be elicited, however, when conduction through the local neuromuscular mechanism was arrested by compression of the wall of the proximal portion of the duodenum between a ligature on the outside and a solid cylindrical body in the lumen. Obviously, this reaction may, at least in the

absence of intact extrinsic nerves, be carried out as a reflex through the local neuromuscular mechanism.

According to Bayliss and Starling (1899, 1900), stimulation of the small intestine usually results in contraction above and relaxation below the point at which the stimulus is applied. The most efficient stimulus for this reaction is a bolus in the lumen of the intestine. The contractions initiated by the bolus tend to be propagated along the intestine and to displace the bolus aborally. This reaction also occurs following bilateral section of the extrinsic nerves, but is abolished by nicotine and certain other drugs when administered in doses which were regarded by Bayliss and Starling as sufficient to paralyze the enteric nervous system. They, therefore, regarded peristalsis in the small intestine as a local reflex phenomenon. As observed by Cannon (1912), peristaltic waves are interrupted by an incision around the small intestine which divides both the longitudinal and circular muscle layers. Such an incision divides the myenteric plexus. Cannon also observed the reflex described by Bayliss and Starling in excised pieces of the stomach and intestine, and designated it the "myenteric reflex."

Alvarez and Zimmerman (1927) advanced certain experimental data which seem to indicate that peristaltic contractions of the intestine are not always accompanied by inhibition below the point of stimulation. On the basis of a careful study of successive pictures of a cinema film taken of the rabbit's bowel, under a bath of salt solution, during the progress of peristaltic rushes, they concluded that "what looks occasionally like descending inhibition is really distention, due to the advanced column of intestinal contents." They conceded, however, that descending inhibition may precede peristaltic contraction under certain conditions.

Exner (1902) observed that sharp metallic objects, *e. g.*, pins and needles, introduced into the digestive tube of experimental animals with their food, not infrequently pass through and are discharged in the feces without having penetrated the gastro-intestinal wall or injured the mucous epithelium. On examination of the intestine while pins and needles were passing through it, these objects were commonly found lying in longitudinal grooves in the mucosa, the majority of the pins being located with the head aborally. According to Exner, the stomach and intestine possess in the muscularis mucosæ a mechanism which is adapted to protect the epithelium against injury by pointed foreign bodies. When a pointed body touches the epithelium it forms a groove, *i. e.*, the epithelium evades the pointed object and effects contact with the foreign body in a manner which is least likely to cause injury. In a study of the motility of the muscularis mucosæ and the intestinal villi, King and Arnold (1922) described retraction of the villi and ridging and pitting of the mucosa in response to mechanical and chemical stimuli

applied to the intestinal epithelium. These phenomena also occurred following section and degeneration of the splanchnic nerves. Since no apparent reaction of the intestinal villi could be elicited by vagus stimulation, these authors concluded that vagus fibers do not reach the muscularis mucosæ. They interpreted the reactions of the mucosa and villi to stimulation of the intestinal epithelium as local reflexes mediated through the local neuromuscular mechanism.

After studying the motility of the large intestine following section of the extrinsic nerves, Bayliss and Starling (1900), Elliott and Barclay-Smith (1904), and Langley and Magnus (1905) all concluded that peristalsis in the large intestine also involves a local reflex mechanism. In animals in which the spinal cord had been destroyed, Lyman (1913) observed that antiperistalsis in the large intestine ceases when food material enters it from the ileum. This also involves reflex activity of the enteric nervous system. Furthermore, as pointed out above, the defecation reflex may be restored following destruction of the spinal center through which it is normally controlled.

The various gastro-intestinal reactions just referred to and certain others are commonly regarded as reflex activities. Inasmuch as all these reactions may be carried out following section of the nerves through which they might be mediated as cerebrospinal reflexes, it must be conceded that the enteric nervous system includes mechanisms through which coördinated reflexes can be carried out.

Rhythmic Gastro-intestinal Contractions.—Not a little experimental evidence has been advanced which seems to indicate that the purely rhythmic contractions of the gastro-intestinal musculature are myogenic. According to Bayliss and Starling (1899), the rhythmic contractions of the small intestine persist following the administration of drugs in doses which they regarded as sufficient to paralyze the myenteric plexus. They also observed that, under these conditions, waves of contraction which, unlike peristaltic contractions, are not preceded by inhibition, advance indifferently in either direction along the small intestine. According to Elliott and Barclay-Smith (1904), antiperistalsis in the large intestine persists following the administration of nicotin in doses sufficient to abolish peristalsis in the small intestine. According to Cannon (1909), gastric peristalsis persists following the administration of nicotin in large doses or multiple incisions through the muscular layers of the stomach which he regarded as sufficient to interrupt the continuity of the myenteric plexus. He also observed that the rhythmic contractions in the small intestine are not abolished by multiple incisions through the muscular layers (Cannon, 1912).

Bayliss and Starling (1899) advanced the theory that the rhythmic contractions of the intestine, *i. e.*, those which persist after the

coördinated movements which they regarded as reflex are abolished, are myogenic. This conclusion may be essentially correct, but it cannot be regarded as fully substantiated by the results of their experimental work with nicotine. The inference that the enteric plexuses are no longer functional following abolition of the myenteric reflex is untenable. As observed by King and Arnold (1922), responses of the intestinal villi to chemical and mechanical stimulation of the intestinal epithelium are not abolished by nicotine until it is present in sufficient concentration to paralyze the muscularis mucosæ. They interpreted these reactions as reflexes mediated through the submucous plexus. They seemed to be of the opinion that this plexus is not affected by nicotine in the same manner as, according to current conceptions, other autonomic ganglia are affected by this drug. Neither were they convinced that nicotine paralyzes the myenteric plexus. Thomas and Kuntz (1926) have shown that the influence of the vagus on the small intestine, as judged by the motor effects of vagus stimulation, is not abolished by doses of nicotine many times as large as the dosage which, in the experiments of Bayliss and Starling, abolished the peristaltic reflex. The dosage employed by Bayliss and Starling (2 to 3 cc. of a 1 per cent solution for a small dog), if not increased, holds the manifestation of the typical effects of vagus stimulation in abeyance. When nicotine is administered in greatly increased doses, vagus stimulation again becomes effective and remains so until the drug is present in a concentration representing 2 to 3 grams of the undiluted alkaloid per kilogram of body weight (Thomas and Kuntz, 1926). This finding was confirmed by Mulinos (1927). Obviously, the small dosage of nicotine employed by Bayliss and Starling does not paralyze the vago-enteric mechanism, but holds certain of its functions in abeyance, probably by a process of inhibition. Consequently, the results of the experiments of Bayliss and Starling do not demonstrate the myogenic nature of the rhythmic contractions which persist following abolition of the myenteric reflex by small doses of nicotine.

The experimental results recorded by Magnus (1905), Gunn and Underhill (1914), and Alvarez and Mahoney (1922) are more convincing, but not conclusive. These investigators took advantage of the fact that the longitudinal muscle, with the major portion of the myenteric plexus adhering to it, and the submucosa, including the submucous plexus, may be separated from the circular muscle. They proceeded on the assumption that circular muscle isolated in this manner is practically free from nervous elements, especially if only the deeper layers are retained. All these investigators observed rhythmic contractions in strips of intestinal muscle isolated in this manner, although Magnus observed them only after the use of stimulating drugs. These results were interpreted as indicating

that intestinal muscle may contract rhythmically in the absence of nervous influences at least under certain conditions. This interpretation was criticized recently by van Esveld (1928) on the basis of his observations on preparations of the intestine of the cat which revealed the existence of ganglion cells imbedded in the circular muscle layer. In view of this finding, it cannot be assumed that any portion of the circular muscle is completely denervated by mechanical separation. Even though complete denervation could be assumed, the results reported by the investigators named above would not prove that the rhythmic contractions of the gastro-intestinal musculature in the intact animal are independent of nervous control.

Certain experimental data seem to indicate that, in the presence of the intact enteric nervous system, even the rhythmic contractions of the gastro-intestinal musculature are subject to nervous influences. According to Roger (1906), the strength of the rhythmic segmenting contractions in the intestine is influenced by the nature of the intestinal content. He observed that the segmenting contractions were weaker when the intestine was filled with a sodium chloride solution than when it was filled with a solution of sugar or peptone. Yanase (1907) also reported that he was unable, in embryos of the guinea-pig, to observe spontaneous movements of the digestive tube until the myenteric plexus had developed.

In a recent experimental study involving the use of nicotin in massive doses, Thomas and Kuntz (1926) have shown, in the intact animal and in excised pieces of the stomach and intestine, that rhythmic gastric and intestinal contractions persist following complete paralysis of the enteric nervous system, but the kymographic records of these contractions differ characteristically from the records of rhythmic contractions obtained while the enteric nervous system remains functional. In so far as the result of these experiments indicate that the gastro-intestinal musculature possesses the inherent capacity to contract rhythmically, they corroborate the findings of those investigators who regard the rhythmic contractions of the stomach and intestine as myogenic, but they neither indicate that these rhythmic contractions are normally carried out without nervous control, nor that the gastro-intestinal musculature could adequately perform even its simpler motor functions in the absence of nervous influences. The rhythmic gastro-intestinal contractions, which persist after the enteric nervous system is paralyzed, differ widely from those carried out in the unpoisoned organs. The records of even the simplest forms of rhythmic activity in an unpoisoned segment of the intestine, in which functional activity of the enteric nervous system may still be assumed, are characterized by frequent changes in tonus and amplitude which show a high degree of variation and complexity. None of these irregularities

appear in the records obtained following denervation with nicotin. The movements which persist consist of mechanically regular contractions and relaxations. While the records obtained before the administration of nicotin cannot be regarded as representing strictly normal functional activity, the difference between the extremely variable activity of the unpoisoned viscus and the mechanical regularity exhibited by the denervated preparation probably represents in some measure the functional control normally exercised by the enteric nervous system. The frequent changes and irregularities observed in the records of the activity of the unpoisoned viscus under experimental conditions probably represent the functional activity of a nervous mechanism which is capable of bringing about similar changes in an orderly and purposeful sequence under the influence of the stimuli of its natural environment.

As the dosage of nicotin was increased, in both the experiments carried out on excised pieces of the intestine and those carried out with the stomach and intestine *in situ*, the amplitude of the rhythmic contractions increased progressively until the concentration of nicotin became relatively high, and then gradually decreased. Assuming that the influence of nicotin in moderate doses is exerted mainly on the nervous mechanism, this fact suggests a functional relationship of the enteric nervous system to the amplitude of the rhythmic contractions. Since all activity ceased in very high concentrations of nicotin, it seems highly probable that the gradual reduction in the amplitude of the rhythmic contractions after the maximum amplitude was reached, was due to the depressant effect of nicotin in high concentration on the muscle directly. The cause of the progressive increase in amplitude which preceded this depression is less apparent. It may be the primary stimulating effect of nicotin on the muscle preceding the depression. On the other hand, the gastro-intestinal musculature may normally be subject to inhibitory influences exerted by the enteric nervous mechanism. Such inhibitory influences would be removed as soon as the nervous mechanism became materially depressed by nicotin. The fact that preparations of excised intestine which when first set up are quiescent may be thrown into action promptly by the administration of sufficient nicotin to materially depress the nervous mechanism, favors the latter possibility. Probably both stimulation of the muscle and removal of nervous inhibition play a part in the phenomenon in question.

The rate of the contractions is not increased in proportion to the increase in amplitude as the dosage of nicotin is increased. Neither does nervous stimulation exert a constant effect on the rate of contraction. On the other hand, the depressant effect of nicotin in high concentration affects both the amplitude and the rate of the contractions. These facts suggest that the effect of removal

of inhibition may be quantitatively greater than the effect of direct stimulation of the muscle in increasing the amplitude of contraction. They also suggest that the inhibition, which is generally regarded as responsible for the quiescence of the gastro-intestinal musculature, so commonly observed following operative procedures or manipulation of these organs, is not the result of reflexes involving the extrinsic nerves alone, but is, as Bayliss and Starling assumed, in part the result of inhibitory influences exerted by the enteric nervous system.

The relative constancy of the rate of the rhythmic contractions as compared with the great variability in tonus and amplitude, under the influence of drug action and nervous stimulation by means of the galvanic current, throughout these experiments suggests that the rate may be quite independent of the nervous influences which bring about changes in tonus and amplitude. The rate of the rhythmic contractions probably depends on properties which are inherent in the gastro-intestinal musculature, and is, therefore, subject to nervous control in a lesser degree than tonus and amplitude.

The results of these experiments seem to indicate quite clearly that the rhythmic gastro-intestinal contractions are myogenic in the sense that they may be initiated and carried out in the absence of nervous impulses, but that they are normally subject to regulatory control which, at least in the absence of functional extrinsic nerves, must be mediated through the enteric nervous system.

Inasmuch as the effect of vagus stimulation is held in abeyance and certain of the gastro-intestinal movements are abolished by the effect of nicotin in moderate dosage, it has been assumed by some that any functional activity manifested by the enteric nervous system following the administration of moderate doses of nicotin must be mediated by synaptic nervous mechanisms. In the light of the experimental results here cited, this assumption is unnecessary. As we have seen, when the dosage of nicotin is progressively increased, vagus stimulation, the effect of which was held in abeyance by the smaller doses of nicotin, again becomes effective and remains so until nicotin is present in sufficient concentration to paralyze the enteric nervous mechanism (Thomas and Kuntz). Consequently, there must be synapses in the vagus efferent chains which are as resistant to nicotin paralysis as the neuromuscular junctions themselves. If, as indicated by some of the anatomical data set forth above, some enteric neurons actually make synaptic connections with others, these synapses are probably equally resistant to nicotin paralysis. It seems highly probable, therefore, that whatever functional activity persists in the enteric nervous system following the administration of nicotin in moderate dosage is true reflex activity. This view obviates the necessity both of denying the regulatory nervous control of rhythmic gastro-intestinal contractions

under physiological conditions, and of postulating the existence of asynaptic nerve nets in the enteric nervous system.

In view of the fact that the coördinated reflex activities of the gastro-intestinal musculature may be carried out apparently according to their normal physiological mode in the absence of central nervous influences, the enteric nervous system must be regarded as more complex both in its anatomical structure and physiological functions than other peripheral plexuses, *e. g.*, the cardiac and pulmonary plexuses. It seems most reasonable to regard it as a reflex system capable of independent coördinated reflex activity, but subject to reflex motor and inhibitory influences through the central nervous system.

Nervous Regulation of Intestinal Secretion.—Data regarding the rôle of nervous influences in intestinal secretion are meager, but isolated facts which indicate that nervous impulses play an important part in regulating the secretory activity of the intestinal glands are not wanting. Under normal conditions, the secretory activity of the intestinal glands depends in a large measure on the intestinal contents. The glands in the small intestine normally secrete very little or not at all while the intestine is at rest. Mechanical stimulation of the mucosa, however, calls forth an immediate flow of secretion from these glands. The quality of this secretion also depends on the character of the mechanical stimulus employed. In Glinski's (1891) experiments, the introduction of a pledget of wool into the intestine through an artificial opening, and its passage to another artificial opening farther distally, resulted in the production of a watery secretion containing very little mucus. On the other hand, the introduction of dry peas through the same opening, and their passage to the more distal opening resulted in the production of a less watery secretion containing much more mucus. In general, glandular activity elicited by direct mechanical stimulation of the intestinal mucosa involves only a localized area of the intestine. This fact strongly suggests that the reflex mechanisms employed involve only neurons in the enteric plexuses.

Sawitsch and Soshestivensky (1917, 1921) were able to demonstrate a secretory influence of the vagus on the intestinal glands in spinal animals (cats). In their experiments, vagus stimulation resulted in an increase in both the liquid and enzyme content of the intestinal secretion, but the effect was most marked on the secretion of enzymes. Within certain limits, the enzyme content of the intestinal secretion increased with increasing strength of stimulation, regardless of the quantity of liquid secreted. Administration of atropin in moderate doses resulted in diminution of the secretory effect of vagus stimulation, and, in large doses, abolished it entirely. Abolition of the secretory effect of vagus stimulation on the intestinal glands, however, required larger doses of atropin than abolition of

the vagus effect on intestinal motility. This finding was regarded by Sawitsch and Soshestivensky as supporting the theory that secretory activity of the intestinal glands and intestinal motility are independent of each other.

Section of the extrinsic nerves supplying a given portion of the intestine is followed by continuous secretory activity of the glands in that portion. This has been called paralytic intestinal secretion. Possibly the vasodilatation which follows section of the extrinsic nerves is a factor in the output of intestinal secretion under these conditions. Molnar (1909) advanced experimental data, however, which indicate quite clearly that the abundant and continuous secretory activity of the intestinal glands, following section of the extrinsic nerves of the intestine, is due mainly to the elimination of normal inhibitory nervous influences. These data, like the data bearing on the effects of vagus stimulation, suggest that the secretory activity of the intestinal glands is normally subject to a measure of regulatory nervous control.

That intestinal secretion is regulated in part by the intestinal content and substances circulating in the blood is well known. Molnar (1909) was able to show that the intravenous injection of meat extractives in dogs results in increased intestinal secretion. Yet, in the intact animal, the intestinal glands do not secrete continuously, even though the stimulating substances in the blood are increased by artificial means. Molnar's experimental results led him to conclude that the intestinal gland cells are continuously influenced directly by hormones circulating in the blood, but their secretory activity is normally held in check by inhibitory nervous influences. Brestkin and Sawitsch (1927) also supported the theory that the nervous regulation of the secretory activity of the intestinal glands consists mainly in inhibition. This is also in full accord with the discovery of Volborth (1925), that secretin is a normal constituent of the intestinal juice.

CHAPTER X.

INNERVATION OF THE BILIARY SYSTEM.

EXTRINSIC NERVES OF THE BILIARY SYSTEM.

THE nerve supply to the liver is derived through the celiac plexus, the vagi, and the phrenic plexus. The majority of the nerve fibers

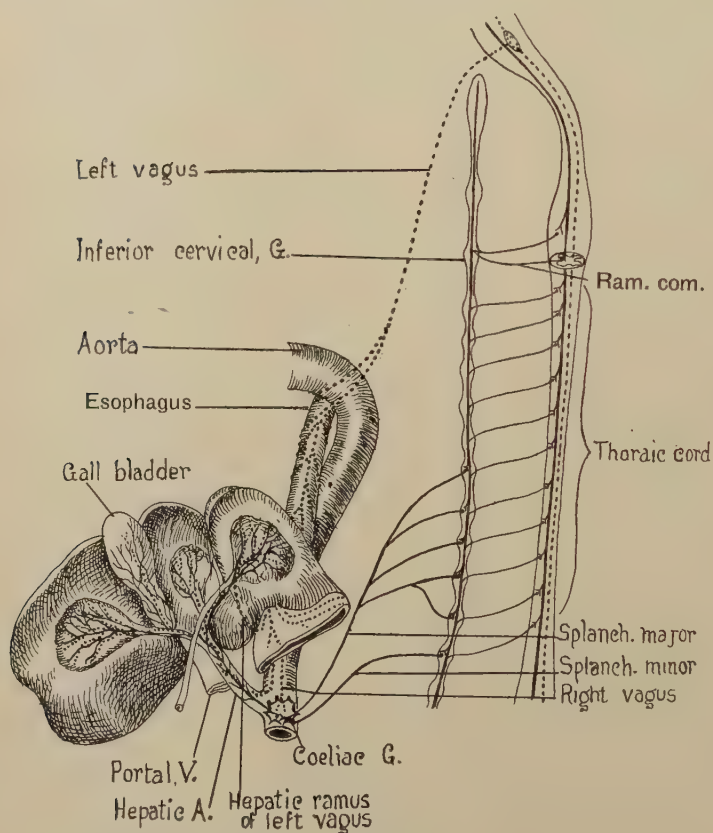


FIG. 46.—Diagram illustrating the distribution of sympathetic and parasympathetic nerves to the biliary system. Sympathetic nerves indicated by continuous, and parasympathetic nerves indicated by dotted lines. (Modified from Greving.)

distributed to the biliary system and portal vessels are sympathetic in origin and reach the hepatic portal through the coeliac plexus.

According to Greving (1924), no rami join the liver directly from the sympathetic trunks in man. The nerves approaching the liver from the coeliac plexus give rise to the hepatic plexus which, according to Raigorodsky (1928), may be subdivided into the anterior and posterior hepatic plexuses. The anterior hepatic plexus lies in relation to the hepatic artery; the posterior hepatic plexus arises just above the origin of the hepatic portal vein, where it lies in proximity to the anterior plexus. It deviates to the right as it extends upward along the portal vein and bile duct to the liver, which it enters in the vicinity of the right branch of the hepatic artery (Raigorodsky, 1928). The anterior and posterior hepatic plexuses are connected by frequent anastomosing branches.

As the left vagus passes downward along the anterior aspect of the esophagus, it gives rise to three main divisions. The left and middle divisions are distributed mainly to the stomach; the right division to the liver. The major portion of this division, including several rami, joins the liver through the hepato-gastric ligament. These rami do not enter the hepatic portal, but are distributed mainly to the left hepatic lobe. Some of them communicate with the anterior hepatic plexus. Other hepatic rami of the left vagus join the coeliac ganglion. As the right vagus enters the abdomen on the posterior aspect of the esophagus, the major portion of its fibers enter the coeliac ganglion; one or more slender branches pass over the coeliac ganglion and, becoming incorporated in the hepatic plexus, enter the hepatic portal. A branch of the right vagus usually joins the hepatic branch of the left vagus in the hepato-gastric ligament.

The phrenic nerve supplies branches to the liver only after anastomosing with sympathetic nerves. According to Raigorodsky (1928), some of these branches enter the liver near the posterior border; others through the hepatic portal. Not infrequently branches of the phrenic nerve anastomose with hepatic branches of the left vagus.

INTRINSIC NERVES OF THE BILIARY SYSTEM.

As the hepatic artery and portal vein enter the liver, they are accompanied by nerves made up mainly of unmyelinated fibers. These nerves give rise to branches which continue along the branches of the blood vessels and bile ducts. In Golgi preparations, Berkley (1893) described the nerves associated with the hepatic vessels and bile ducts as delicate plexuses, and pointed out that the supply to the hepatic artery is more abundant than that to the portal vein. He also observed nerve fibers which ramify among the liver cells and designated them intralobular nerves. According to Wolf (1902), who studied methylene-blue preparations, the fibers which penetrate

the liver lobules form terminal networks about the liver cells. In preparations of the human liver, Greving (1924) also described nerve fibers in the parenchyma which in some instances form a meshwork about liver cells. He found no ganglion cells either in the hepatic portal or the liver.

According to Dogiel (1895), the gall bladder and bile ducts, including the cystic and common ducts, have a relatively rich nerve supply. Nerve fiber bundles arising from the hepatic plexus accompany the blood vessels into the wall of the gall bladder and bile duct and form a plexus in the outer connective tissue layer from which fibers are distributed to the musculature and the mucosa. This plexus, according to Dogiel, includes numerous ganglion cells which occur either singly or aggregated in small ganglia. The fiber bundles are composed mainly of unmyelinated fibers, some of which arise from the local ganglion cells. Dogiel also described unmyelinated terminal branches of myelinated fibers of extrinsic origin, some of which terminate in the intrinsic ganglia, while others pass through these ganglia. The terminations of the latter could not be observed. According to Greving (1924), the larger nerve bundles in the wall of the gall bladder accompany the arteries, but the smaller fiber bundles form a close-meshed plexus in the musculature. Greving was unable, in his preparations, to find ganglion cells in the wall of the gall bladder.

The preganglionic splanchnic fibers of the hepatic supply make synaptic connections with sympathetic neurons in the celiac ganglion. The location of the parasympathetic neurons is less definitely known. The majority of the preganglionic vagus fibers included in the hepatic supply probably effect synaptic connections with neurons in the hepatic plexus. If, as Dogiel maintained, ganglion cells exist in the walls of the gall bladder and bile ducts, these also belong to the parasympathetic system and probably are components of vagus efferent chains. As stated above, some of the terminal vagus branches do not traverse the hepatic plexus, but enter the liver directly. There are no anatomical data available which prove that efferent fibers in these branches effect synaptic connections with peripheral neurons. Possibly, some of these fibers are the axons of neurons located in the jugular or nodose ganglion. Both the vagus and splanchnic nerves also convey general visceral afferent fibers to the biliary system. The distribution and terminations of these fibers have not been adequately described.

NERVOUS REGULATION OF LIVER FUNCTIONS.

Carbohydrate Metabolism.—That glycogen represents a stage in the production of sugar in the body was maintained by Claude Bernard as early as 1857. Even earlier than this, he had made the

interesting observation that puncture of the floor of the fourth ventricle in a definitely circumscribed area results in hyperglycemia and glycosuria which last for several hours. These observations suggested that nervous influences play a part in the regulation of sugar production from glycogen and that the medulla oblongata contains a center from which this regulatory influence emanates. This center, which may be regarded as the sugar center, is located between the levels of origin of the acoustic and vagus nerves. It involves the area in which the dorsal motor nucleus of the vagus is situated. That the sugar which appears in the urine following puncture of the medullary center in question is derived from glycogen in the liver was also determined by Claude Bernard (1887). He observed that in animals whose supply of glycogen had been depleted by continued fasting, puncture of the sugar center was not followed by glycosuria or hyperglycemia. He also observed that section of the spinal cord in the lower thoracic region does not prevent glycosuria following puncture of the sugar center, but that such puncture has no influence on the conversion of glycogen into sugar following section of the spinal cord in the upper thoracic region. He concluded, therefore, that puncture of the medullary center in question stimulates sugar production only in the liver and that the efferent impulses which bring about this result are conveyed to the liver through the splanchnic nerves. The results of more recent experiments indicate that these impulses leave the spinal cord in the fifth and sixth thoracic segments. That the liver is the seat of the increased sugar production following puncture of the sugar center is also indicated by the fact that glycosuria does not follow this operation when the hepatic vessels are ligated.

The so-called sugar center probably receives a constant influx of afferent impulses, particularly through the vagi, which play an important rôle in the regulation of the normal production of sugar in the liver. Pflüger (1903) advanced the theory that the body is, by virtue of this reflex mechanism, enabled to draw upon the food supply represented by the glycogen in the liver whenever an increased expenditure of energy is required. For example, when a particular group of muscles has, through prolonged activity, exhausted its local food supply, afferent impulses are conveyed to the medulla which activate the sugar center and thus bring about the release of energy-producing food material for immediate use.

Claude Bernard advanced the theory that stimulation of the sugar center in the medulla gives rise to vasomotor changes which result in increased circulation in the liver and that the increased blood supply brings about increased secretory activity. On the contrary, Pflüger (1903) expressed the opinion that sugar production is controlled, not by vasomotor changes, but by secretory nerves. Blum (1901) observed that subcutaneous injection of adrenalin

results in marked glycosuria. Furthermore, adrenalin brings about the conversion of glycogen into sugar in the fresh excised liver. According to Meyer (1906), puncture of the sugar center does not result in glycosuria following bilateral adrenalectomy. This seemed to indicate that puncture of the sugar center does not affect the liver function through direct nervous influences, but brings about the liberation of adrenalin, which in turn stimulates the production of sugar in the liver. Starkenstein (1912), however, reported the production of glycosuria by afferent vagus stimulation in animals which had previously been subjected to bilateral adrenal extirpation.

The apparently contradictory results of Meyer and Starkenstein are readily reconciled in the light of results obtained by Freund and Marchand (1904). These investigators found that puncture of the sugar center in animals which had previously been subjected to bilateral adrenalectomy was followed by hyperglycemia, although they found no sugar in the urine. It may be assumed, therefore, that puncture of the sugar center results in a direct nervous influence on the liver which is sufficient to produce hyperglycemia, even though it does not produce glycosuria, and that in animals with adrenals intact the same stimulus results in glycosuria because the effect of the adrenalin liberated is added to the direct nervous influence. According to this view, stimulation of the sugar center gives rise both to impulses which are conveyed to the liver cells directly and impulses which are conveyed to the adrenals, resulting in internal secretory activity. The adrenalin discharged into the blood probably influences the liver cells by reason of its action on the sympathetic fiber terminations. Certain experimental data advanced by Clark (1928) seem to indicate that autonomic nervous influences play no part in the production of hyperglycemia induced by the intravenous injection of pituitrin.

The production of glycogen, like the conversion of glycogen into sugar, is regulated by both nervous and endocrin influences. Vagus stimulation brings about increased internal secretory activity of the pancreas, but also results in hyperglycemia (Asher and Correl, 1918). On the other hand, injection of pancreatic extract inhibits the conversion of glycogen into sugar. According to Eiger (1915), however, vagus stimulation, in turtles which had previously been subjected to extirpation of the pancreas, also resulted in increased glycogen production. These experimental results seem to justify the conclusion that the vagus includes fibers which, through their direct action on the liver cells, augment glycogen production, and fibers which augment the internal secretory activity of the pancreas, and thus indirectly influence the functional activity of the liver cells. The effect of both these influences is an increase in the glycogen content of the liver and inhibition of sugar production.

In a recent experimental study on rabbits involving the adminis-

tration of adrenalin and insulin, Dresel and Omonsky (1927) observed lowered adrenalin hyperglycemia and heightened insulin hypoglycemia following bilateral vagus section. Bilateral section of both splanchnic and vagus nerves, in their experiments, resulted in diminished adrenalin hyperglycemia and markedly increased insulin hypoglycemia. In general, impulses mediated through the sympathetic nerves augment the conversion of glycogen into sugar, and impulses mediated through the vagi bring about an increase in the glycogen content of the liver. In both cases, the liver function is influenced by the direct action of nervous impulses and by the indirect effect of changes brought about in the activity of the appropriate internal secretory organs, viz.: the adrenals and pancreas. This reflex regulation of carbohydrate metabolism in the liver is of primary physiological importance in maintaining the sugar content of the blood within the range of normal variation. According to Toenniessen (1924), variations in the concentration of sugar in the blood constitute the chief physiological stimuli to the sugar center. Injury to this center results only in temporary glycosuria. Frank diabetes mellitus caused by a primary lesion of the sugar center has not been demonstrated. This condition probably is always the result of disease of the peripheral organs involved in carbohydrate metabolism, particularly the pancreas.

Protein Metabolism.—That nervous influences also play a rôle in protein metabolism in the liver is clearly indicated by the results of experimental studies, particularly those of Freund and Grafe (1912). According to their findings, protein metabolism in the liver is augmented by impulses mediated through the sympathetic, and inhibited by impulses mediated through its parasympathetic nerves. The cerebrospinal centers involved are located in the diencephalon.

According to Toenniessen (1924), the three factors involved in protein metabolism in the liver, viz.: nervous excitation, nervous inhibition, and the inherent capacity of the liver cells to break up proteins are so adjusted, under normal physiological conditions, that the inhibitory influence of the parasympathetic nerves outweighs the excitatory influence of the sympathetic nerves and holds the inherent tendency of the liver cells to metabolize protein in check. Suppression of the parasympathetic impulses or sympathetic stimulation, therefore, results in increased protein metabolism. Increased protein metabolism in the liver does not involve destruction of the protoplasm of the liver cells, but is brought about at the expense of stored protein.

Bile Secretion.—Nervous influences in the regulation of bile production were unknown to the older physiologists. Even Heidenhain (1883) found no evidence that the secretion of bile is in any way subject to nervous influences. The results of recent investigations, however, show clearly that this function of the liver is also subject

in some degree to regulatory nervous influences. Eiger (1916) was able to show that intrathoracic stimulation of the vagus distal to its cardiac branches in the dog brings about increased productions of bile. He also pointed out that the ratio of water to the other normal constituents of the bile was not materially affected by vagus stimulation. According to Eiger, the influence of the vagus on bile secretion is that of a true secretory nerve. Although a direct effect of sympathetic stimulation on bile production was less evident, Eiger's results indicate that the sympathetic nerves exert an inhibitory influence on the secretion of bile. In addition to nervous influences, doubtless, direct chemical stimuli and the effects of hormones play an important part in the regulatory control of bile secretion.

NERVOUS INFLUENCE ON GALL BLADDER AND BILE DUCTS.

In the absence of any mechanism by which the opening of the common bile duct into the duodenum could be closed, bile entering the hepatic ducts would flow directly into the intestine. Contraction of the sphincter at the duodenal end of the bile duct or tonic contraction of the duodenum prevents the flow of bile into the intestine and brings about the filling of the gall bladder. According to the older teaching, the gall bladder empties itself by active contraction of its musculature, which is accompanied by relaxation of the sphincter papillæ. Bainbridge and Dale (1908) showed clearly that the vagus fibers distributed to the musculature of the biliary system subserve a motor function. Vagus stimulation usually results in contraction of the gall bladder and relaxation of the sphincter papillæ. According to Rost (1913), the sphincter papillæ relaxes with each contraction of the gall bladder. On the contrary, Eiger (1916) reported that vagus stimulation in the dog, in his experiments, sometimes resulted in contraction of the common bile duct and biliary stasis. This observation seems to be at variance with the foregoing, but it does not militate against the accuracy of the earlier observations, since closure of the bile duct resulted from vagus stimulation only in some cases. If the closure of the bile duct in these instances actually involved contraction of the sphincter papillæ, this result probably indicated that the sphincter papillæ, like the cardiac sphincter, receives both motor and inhibitory fibers through the vagi. It seems highly probable that any stimulus which brings about contraction of the gall bladder would, in general, also be a factor in bringing about the relaxation of the sphincter papillæ, thus opening the way for the expulsion of the bile into the intestine.

Westphal claimed to have actually observed the discharge of bile from the gall bladder into the duodenum in response to vagus stimulation. According to Boyden (1927), merely drinking a glass of water usually results in a discharge of bile from the gall bladder in man. Boyden and Parmacek (1928) reported dilatation of the gall bladder in one case following the drinking of a glass of water. Since the dilatation took place almost immediately, it was regarded as a reflex inhibitory response, probably dependent on a functional imbalance of the autonomic nervous system.

In general, the sympathetic innervation of the musculature of the biliary system subserves an inhibitory function. In the experiments of Bainbridge and Dale (1908), splanchnic stimulation resulted in relaxation of the gall bladder. They also observed augmentation of the rhythmic contractions of the gall bladder following bilateral section of the splanchnics. According to Westphal, splanchnic stimulation inhibits the rhythmic contractions of the gall bladder as well as the peristaltic contractions of the bile duct and also brings about contraction of the sphincter papillæ. He also reported that he could observe spontaneous motor activity of the gall bladder and bile duct following section of both vagus and splanchnic nerves.

These experimental observations seem to justify the conclusion that the musculature of the biliary system, in general, responds to vagus and splanchnic stimulation in essentially the same manner as the gastro-intestinal musculature and that the automatic motor activity of the gall bladder and bile duct, under reflex regulatory control, brings about the discharge of bile from the gall bladder into the duodenum at intervals determined by the passage of food from the stomach into the intestine. That the parasympathetic nerves exert a motor, and the sympathetic nerves an inhibitory effect on the biliary system may be regarded as an established fact. The results of certain recent experimental studies do not, however, support the theory that the gall bladder empties itself by the active contraction of its musculature, nor that it is emptied every time food enters the duodenum.

It has been quite generally assumed that the flow of bile from the gall bladder into the intestine is influenced by the passage of food into the duodenum and by the stimulating effect of substances secreted by the intestinal glands. The results of certain recent experimental studies indicate quite clearly that the discharge of bile from the gall bladder is elicited by the passage of certain kinds of food into the duodenum, but they also seem to indicate that the gall bladder itself plays a more or less passive rôle in the emptying process. It has been maintained, on the basis of experimental findings, that the resistance to the flow of bile into the intestine is brought about by the tonicity of the duodenum and not by the

active contraction of the sphincter papillæ (Burget, 1925, 1926; Graham, 1926). On the other hand, Higgins and Mann (1926) and Whitaker (1926) obtained experimental evidence which seems to indicate that contraction of the sphincter papillæ is a factor in the filling of the gall bladder.

Regardless of whether the resistance to the flow of bile into the intestine is brought about solely by the tonicity of the duodenum or in part by contraction of the sphincter papillæ, the bile is forced into the gall bladder by the secretory pressure of the liver. This pressure may even bring about distention of the filled gall bladder. Assuming the correctness of the theory that the gall bladder empties itself by active contraction of its musculature elicited by reflex nervous stimulation, we should expect this viscus, when in a balanced physiological state, to respond reflexly to the motor activity of the duodenum, stretching of its own musculature, and hormones which might be produced in the intestine. The results of certain recent experimental investigations fail to indicate that any of these stimuli are adequate to elicit reflex contraction of the musculature of the gall bladder which is sufficiently powerful to force the bile into the intestine. In Burget's (1927) experiments, the spontaneous tonus changes in the gall bladder seemed to bear no direct relationship to peristalsis in the duodenum. Burget also concluded, on the basis of his experiments, that drugs which act on the gall bladder through its nerve supply exert little influence on its tonus changes. Furthermore, vagus stimulation which caused contractions of the small intestines had little effect on the gall bladder.

Certain experimental data advanced recently indicate that emptying of the gall bladder is determined in a large measure by the fatty constituents of the ingested food. In Boyden's (1925) experiments, cats fed on a diet of egg yolk and heavy cream "at once exhibited a functional periodicity of the gall bladder in relation to meals." The gall bladder did not undergo any marked changes in volume, in his experiments, while the animals were fed on a pure protein and carbohydrate diet. Boyden also demonstrated the effectiveness of fatty food, particularly egg yolk and cream, in emptying the gall bladder in man. One hour and forty minutes after the beginning of a meal consisting of the yolks of 4 eggs and $\frac{1}{2}$ pint of cream, cholecystograms showed that the gall bladder had shrunk from the fully distended condition brought about by going without food for eighteen hours, to a condition in which it was nearly empty. One hour later, the gall bladder apparently was empty.

Whitaker (1926), McMaster and Elman (1926), Lohner (1926), and Boyden (1926, 1928) reported certain experimental results which they interpreted as indicating that active contraction of the gall bladder is a factor in expelling its contents in the experimental

animals (cats and dogs) in question. Kalk and Schondube (1926) concluded, on the basis of results obtained in their experimental studies of the effect of hypophyseal extract on the gall bladder in the dog, that this viscus is capable of contracting to the extent of expelling its entire content. They described the reaction of the gall bladder to hypophyseal extract as a tonic contraction which involves mainly the corpus and fundus. According to their observations, the flow of bile begins suddenly and continues rapidly until the gall bladder is empty.

Contrary to the positive findings cited above, Auster and Crohn (1922) were unable, by the use of electrical stimulation far stronger than necessary to cause contraction of the small intestine, to elicit any apparent contractions of the gall bladder. Neither could Winkelstein and Aschner (1925), either by reflex or direct stimulation, elicit contractions of the gall bladder which seemed to them adequate to expel its contents. Graham (1926) also cited certain results of experiments carried out by Copher and Kodama which seem to indicate that whatever active contraction of the musculature of the gall bladder may take place, it cannot play more than a minor rôle in emptying the gall bladder. Copher and Illingsworth (1927), on the basis of further experimentation, concluded that emptying of the gall bladder is accomplished in part by contraction of its musculature and in part by other factors. On the basis of an extensive experimental investigation and consideration of the relatively meager development of the musculature of the gall bladder, Burget (1927) concluded that this viscus is incapable of contractions which could play a major rôle in the flow of bile.

Although not a few recent investigators were unable, on the basis of their findings, to support the theory that bile is expelled from the gall bladder by active contraction of its musculature, the weight of evidence available at present favors this theory. On the basis of his own findings and a review of the literature, Boyden (1928) concluded: "It seems reasonable to assume that in the cat, dog, guinea-pig, and man bile is expelled primarily by the contractile force of the muscle tunic of the gall bladder." Data regarding the various factors which determine the flow of bile from the gall bladder are as yet meager, but that reflex nervous influences play an important rôle cannot be denied. It is also well known that influences emanating from the central nervous system, under certain conditions, profoundly affect the biliary system. Strong emotional disturbances, *e. g.*, rage or fright, may give rise to temporary icterus. This probably is due in part to biliary stasis caused by closure of the common bile duct either by increased tonicity of the duodenum or contraction of the sphincter papillæ. Furthermore, the same central nervous influences which bring about biliary stasis may also

bring about increased secretory activity of the liver cells. Under these conditions bile is absorbed into the blood with resulting icterus. The peripheral pathways involved in this reaction are mainly vagus. Emotional icterus, therefore, falls within the realm of vagotonia. Conversely, disturbances of the biliary system, especially gall bladder disease, may give rise to afferent impulses which result in reflex vomiting, tachycardia, regional pruritis, perspiration, dyspnea, salivation or inhibition of salivary secretion, and pupillary disturbances (Thies, 1917). These are all symptoms which indicate far-reaching and profound disturbances of the autonomic nervous system.

CHAPTER XI.

INNERVATION OF GLANDS.

THE SWEAT GLANDS.

Anatomical Data.—The sweat glands are innervated through the thoracolumbar sympathetic outflow. Certain experimental data have been advanced which were interpreted as indicating that these glands also receive parasympathetic fibers (Dieden, 1915), but these data, which will be referred to below, are inconclusive. The sympathetic fibers supplying the sweat glands arise in the ganglia of the sympathetic trunks. Those distributed to the skin of the head and face arise mainly in the superior cervical ganglion, traverse the carotid plexuses, and join the respective cutaneous nerves through which they reach the sweat glands. Throughout the rest of the body, the sympathetic fibers supplying the sweat glands join the spinal nerves via the gray communicating rami and reach their peripheral destination through the cutaneous branches of these nerves. By reason of the distribution of the preganglionic components of the upper thoracic nerves to the cervical sympathetic ganglia, the spinal centers for the innervation of the sweat glands of the entire head, neck, upper extremities, and upper portion of the thorax are located in the upper thoracic segments of the spinal cord. Likewise, by reason of the downward distribution of the preganglionic fibers in the lower portions of the sympathetic trunks, the spinal centers for the innervation of the sweat glands of the lower extremities and the lower portion of the trunk are located in the lower thoracic and upper lumbar segments of the spinal cord. In a recent study carried out on soldiers with spinal cord lesions, André-Thomas was able to show that the spinal centers for the innervation of the sweat glands of the head, neck, and upper thoracic segments are located between the eighth cervical and sixth thoracic segments, those for the upper extremities in the fifth, sixth and seventh thoracic segments, and those for the lower extremities in the lower thoracic and upper lumbar segments of the spinal cord. According to Böwing (1924), the centers for the innervation of the sweat glands and other vegetative cutaneous organs in the region of the anus and external genitalia are located in the sacral portion of the spinal cord.

The simplest reflex arc involved in the reflex activity of the sweat glands may be conceived as follows: the afferent limb consists of an

afferent spinal nerve component which terminates peripherally in a cutaneous sense organ, and the efferent limb of a preganglionic neuron located in the intermediolateral cell column and a sympathetic neuron located in a ganglion of the sympathetic trunk (Fig. 47). If both afferent and efferent limbs are components of the same or adjacent nerves, it may be assumed that the central connection is effected within the segments in question. If, as in the case of the sweat glands in the head region, the afferent and efferent limbs of the reflex arcs are connected with the central nervous system through widely separated nerve roots, the central reflex connections must be regarded as relatively complex. Reflexes of a higher order carried out through afferent and efferent components of the same or adjacent spinal nerves also involve a center in the brain stem, probably the autonomic center in the diencephalon.

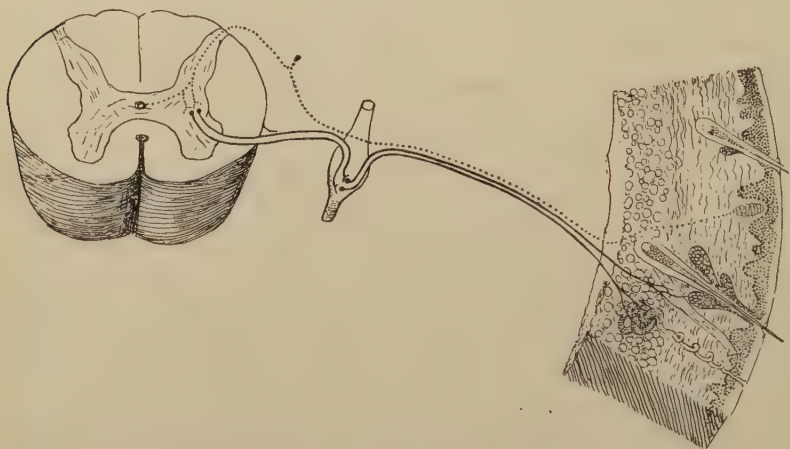


FIG. 47.—Diagram illustrating the innervation of the sweat glands and erector pili muscles.

The sweat glands are simple tubular structures, the terminal portions of which are coiled to form more or less compact knots and contain the secretory cells. The ducts are provided with a thin layer of smooth muscle which may possibly play a rôle in expelling the secretion. This muscle, like other smooth muscle in the skin, is supplied by sympathetic fibers. The secretory fibers to the sweat glands terminate in direct relation to the gland cells.

In man, sweat glands are distributed over the entire surface of the body, but are more abundant and larger in certain areas than in others. They are especially abundant in the head, face, axillæ, palms, soles, and genital region. These are the regions of the body in which perspiration is usually most profuse. In many of the hairy mammals, sweat glands occur only in restricted areas of the

skin. Rabbits, rats, and mice are not known to perspire at all. Pigs have functional sweat glands in the region of the snout. Cats normally perspire on their paw pads. Young dogs also perspire on their paw pads, but are said to lose this capacity as they grow older. Certain other mammals, *e. g.*, the horse, exhibit a general distribution of sweat glands and perspire over the entire surface of the body.

Nervous Regulation of Sweat Secretion.—Unlike many other organs with sympathetic innervation, the sweat glands do not react to direct stimulation, but are activated only by nervous influences. Clinical observations show clearly that section of the cervical sympathetic trunk or extirpation of the superior cervical sympathetic ganglion results in permanent cessation of perspiration in the face on the side of the operation. Likewise, extirpation of any part of the sympathetic trunk or section of the gray communicating rami results in cessation of perspiration in the cutaneous areas deprived of their sympathetic innervation. Following extirpation of the lumbar sympathetic trunks, the skin of the lower extremities remains free from perspiration regardless of the temperature.

The nerves supplying the sweat glands are in a large measure functionally independent of those supplying other vegetative organs in the skin, *viz.*: the cutaneous blood vessels and the erector pili and other cutaneous smooth muscles. The secretory output of the sweat glands is, under ordinary conditions, dependent in a large measure on the cutaneous blood supply, but the sweat glands may exhibit secretory activity even in the absence of cutaneous circulation. This is demonstrated by the fact that nervous stimulation elicits the secretion of sweat in a newly amputated limb. On the other hand, the administration of adrenalin is followed by inhibition of sweat production by reason of the vasoconstrictor action of this drug (Burn, 1925). This is in full accord with the fact of common experience that the secretion of sweat is reduced by chilling of the skin which brings about constriction of the peripheral blood vessels. Burn was also able to show that pilocarpin, a potent sweat-producing stimulant, is ineffective if the capillary dilatation normally brought about by this drug is prevented by section of the spinal nerve roots. In the absence of capillary tonus, pilocarpin is without effect on the cutaneous blood supply. Likewise, it does not affect the secretory activity of the sweat glands, although the postganglionic fibers supplying these glands are still intact. Profuse sweating in man often accompanies a pallid skin, as in terror or nausea. On the other hand, the flushed skin of fever is characterized by the absence of perspiration. All these facts indicate that the sweat glands are excited by the direct action of true secretory fibers, and that this action is quite independent of the functional state of the cutaneous blood vessels and the vasomotor nerves in question.

Under ordinary circumstances, the usual cause of profuse per-

spiration is high external temperature or muscular activity. With regard to the former, it is well known that the high temperature does not stimulate the sweat glands directly, but through the intervention of the central nervous system. Following section of the nerves supplying a limb, exposure of that limb to a high temperature, as by placing it in a warm chamber, does not result in perspiration. Obviously, high temperature alone neither stimulates the sweat glands nor the terminations of the nerve fibers which innervate them. It must be assumed, therefore, that the high temperature stimulates the sensory cutaneous nerves, possibly the heat fibers, and that the sweat glands are excited reflexly through their sympathetic nerve supply. This reflex response plays a very important rôle in the regulation of the body temperature, particularly when the external temperature is high. Although external temperature does not activate the sweat glands directly, it affects their irritability by direct action either on the gland cells or the nerve fiber terminations. If the temperature is below a certain degree, the sweat glands in the cat's paw cannot be excited to secrete at all. Their irritability is very low at low temperature, but increases as the temperature rises up to about 45° C.

Perspiration in response to external temperature is in general limited to the cutaneous areas which are subjected to the high temperature (Dieden, 1915); however, many persons, particularly among the frail and obese, perspire profusely over the entire body when only one arm or one leg is subjected to a high temperature. It must be assumed that exposure of a limited area of the body surface to a high temperature results in an increase in the temperature of the blood, and that increased blood temperature, in these cases, results in stimulation of the autonomic center in the diencephalon through which general excitation of the sweat glands is brought about. This results in a general output of perspiration which tends to prevent any further rise in body temperature.

The spinal centers involved in the innervation of the sweat glands also react to increased blood temperature. This is demonstrated by the fact that, following transection of the spinal cord, perfusion of a portion of the cord below the section with blood heated to 45° C. brings about profuse perspiration in the skin areas innervated from the portion of the spinal cord perfused.

The spinal sweat centers, like the diencephalic center, also react to an increase in the carbon dioxide content of the blood (Müller, 1924). During muscular exercise, both the temperature and carbon dioxide content of the blood are increased by reason of increased oxidation. Probably, both these factors play a part in the activation of the diencephalic and spinal sweat centers from which impulses are conveyed to the sweat glands. The same stimuli also affect the vasomotor center, resulting in peripheral vasodilatation through

which an increased supply of water is made available for elimination through the sweat glands. Thus the output of perspiration is augmented by the vasomotor mechanism.

Afferent stimuli other than temperature may, at least under certain conditions, elicit perspiration. In certain individuals, pungent odors call forth perspiration in the face, and in some instances only on the nose. Electrical stimulation of the brachial plexus in experimental animals not infrequently elicits secretory activity of the sweat glands in both fore limbs. Electrical stimulation of the face also commonly elicits bilateral reflex response of the sweat glands (Dieden, 1918). That painful stimulation, if of sufficient intensity, may result in a sudden outbreak of profuse perspiration over the entire surface of the body is a fact of common experience.

Concentration of the blood by extraction of water through the digestive system does not suppress perspiration completely. Profuse sweating sometimes occurs in cases of violent diarrhea and exhaustion, even when a deficiency of water in the blood and tissues is indicated by profound thirst. Neither does an abundance of water in the blood and tissues exert a marked influence on the output of perspiration. The drinking of cold water in large quantities does not appreciably affect the secretory activity of the sweat glands. On the other hand, the drinking of hot liquids, *e. g.*, hot tea, not infrequently calls forth sudden profuse perspiration.

Psychic Stimulation of Sweat Secretion.—That the sweat centers also react to psychic influences is well known. Strong emotions, particularly anxiety and expectancy, are not infrequently accompanied by profuse perspiration even in persons in good health, but more often in "nervous" individuals. This need not be regarded as essentially pathological. Perspiration during emotional disturbances, however, may assume a pathological aspect. Patients in whom such is the case usually also complain of other nervous disorders, *e. g.*, tachycardia, gastric pains, and headache. Many individuals experience localized perspiration, especially in the palms of the hands, and sometimes also on the soles of the feet during even minor emotional disturbances, such as embarrassment and perplexity. Outbreaks of profuse perspiration without any apparent cause have also been observed in hysterical patients.

Response of Sweat Glands to Cerebral Stimulation.—Cortical stimulation, under certain conditions, also results in excitation of the sweat glands. This fact and the fact that perspiration is a common accompaniment of certain emotional states led certain of the older investigators to conclude that a sweat center exists in the cerebral cortex (Bechterew, 1905). As a result of carefully executed experimental studies, Winkler (1908) concluded that certain cortical fibers arising in the frontal lobe influence perspiration and that these fibers descend through the subthalamic region and cerebral

peduncles into the medulla oblongata. These findings do not, however, prove the existence of a cortical center for the functional regulation of the sweat glands. Certain observations of Dieden (1915) made on hemiplegic patients have an important bearing on this point. These patients, according to Dieden's account, perspired equally on both sides of the body regardless of the extent of the cortical injury which caused the unilateral paralysis. Inasmuch as the hemiplegic conditions in the relatively large number of patients in question were caused by a wide variety of cerebral lesions, he properly assumed that if the secretory activity of the sweat glands were controlled by a cortical center, that center would have been destroyed in some of his patients; consequently, these patients should have exhibited absence of perspiration on one side.

On the basis of observations made on a series of hemiplegic soldiers, Karplus (1916) stated that hemiplegia may be accompanied by increasing perspiration on the paralyzed side. Böwing (1922) observed the same result in patients in whom lesions causing hemiplegia involved the internal capsule. According to Böwing, lesions of the corpus striatum and thalamus, particularly the subthalamus, may also result in increased perspiration on the affected side of the body. Whether these results are to be attributed to stimulation or absence of inhibition of the diencephalic center cannot be stated with certainty. The data available favor the former assumption (Böwing, 1924), but do not indicate the existence of a cortical sweat center.

Direct Influence of Spinal Centers on Sweat Secretion.—Disturbances of perspiration may also be brought about through the sweat centers in the spinal cord. This is well illustrated by the segmentally arranged areas of perspiration in tubercular patients. Outbreaks of perspiration in cases of tetanus must also be regarded as the result of hyperexcitability of the sweat centers in the spinal cord (Böwing, 1924).

Recorded observations on the effect of organic lesions of the spinal cord on the functional activity of the sweat glands are somewhat contradictory. Normal perspiration as well as a decrease in or even cessation of sweat secretion in the paralyzed portion of the body has been reported following transverse lesions of the spinal cord. In a careful study of twelve paraplegic patients, Böwing never observed complete absence of perspiration in the affected areas, but usually found that the secretory activity of the sweat glands in these areas was somewhat diminished. Neither did he find a sharp line of demarcation between the areas of normal and diminished perspiration at the level of the spinal cord lesion in cases in which the lesion was located in the thoracic or lumbar region. This may be explained on the basis of the peripheral distribution of the preganglionic fibers involved in the innervation of the sweat

glands. Some of the preganglionic fibers in question descend in the sympathetic trunk and effect synaptic connections with sympathetic neurons in segments lower than the one in which they emerge from the spinal cord.

Unilateral lesions of the spinal cord are not infrequently followed by diminished perspiration in the affected region on the side of the lesion. Likewise, diseases which involve localized degeneration of spinal cord tissue, *e. g.*, syringomyelia and poliomyelitis, are also accompanied by functional disturbances of the sweat glands in the affected area. Whether such disturbances involve a diminished or an increased output of perspiration depends on the exact site of the lesion and the character of the degenerative process. Destruction of cells in the intermediolateral cell column commonly results in localized anhydrosis.

The Effect of Drugs on Sweat Secretion.—That certain drugs influence the output of perspiration is well known. Their effect is probably exerted through the nerve fibers supplying the sweat glands. A direct effect of drugs on the sweat glands has not been demonstrated beyond question. In experiments on cats, Langley (*Jour. Physiol.*, vol. 56, p. 110) observed a diminished output of perspiration on the hind-paw pad following injection of pilocarpin after the sciatic nerve had undergone degeneration. This finding, which suggests a direct effect of pilocarpin on the sweat glands, was corroborated by Burn (1925). Antipyretic drugs, *e. g.*, the salicylates, probably bring about perspiration by reason of their action on the diencephalic sweat center. Certain other drugs, *e. g.*, strychnin and camphor, exert, their sudorific effect on the spinal sweat centers. Muscarin, physostigmin, and pilocarpin bring about perspiration by reason of their stimulating effect on the terminations of the nerve fibers which supply the sweat glands. Atropin, on the other hand, paralyzes these nerve fiber terminations and, therefore, brings about cessation of perspiration.

Although adrenalin is a powerful stimulant for other organs with sympathetic innervation, it does not bring about secretory activity of the sweat glands. It has even been found to inhibit spontaneous perspiration in certain neurotic patients and to diminish the sudorific effect of pilocarpin (Billigheimer, 1920). According to Freund (1920), adrenalin may, under certain conditions, also exert a stimulating influence on the sudorific mechanism. He found, in certain cases, that areas of the skin which were treated with adrenalin exhibited more profuse sweating than the adjacent areas while in the hot-air chamber. Dieden (1915) reported certain experimental results which seemed to indicate that the stimulating effect of adrenalin on the sweat glands is best developed following interruption of their functional connection with the sweat centers in the central nervous system. During deep anesthesia and following

section of the sciatic nerve or the dorsal roots of the lower lumbar nerves in the cat, according to his observations, the administration of adrenalin was followed by a copious output of perspiration on the hind paws. In experiments designed to test the validity of Dieden's results, neither Langley (1922) nor Schilf and Mandur (1922) were able to detect any appreciable influence of adrenalin injected into the hind paw pads of cats on the secretory activity of the sweat glands, either with intact innervation or following section of the sciatic nerves.

The sweat glands are still excited by nervous stimulation following the administration of ergotoxin (Cushny, 1924), although the sympathetic nerves are paralyzed by this drug. Ergotoxin, however, brings about paralysis of only those end organs which are excited by adrenalin. As stated above, the sweat glands are not excited by the latter drug; therefore, we should not expect paralysis of the sudorific mechanism by ergotoxin. The difference in the reactions of the sweat glands and other sympathetically innervated organs in the presence of ergotoxin and adrenalin shows that these drugs do not exert the same effect on all sympathetic nerves. The fact that neither ergotoxin nor adrenalin exerts an appreciable influence on the secretory activity of the sweat glands, according to Schilf (1926), also affords evidence that the sweat glands contain no receptive substances for either of these drugs.

Are the Sweat Glands Supplied by Inhibitory Nerves?—Throughout the foregoing discussion, it was assumed that the efferent innervation of the sweat glands consists only of secretory fibers of sympathetic origin. The existence of inhibitory fibers of parasympathetic origin to the sweat glands has been maintained, particularly by Dieden (1915-1916), on the basis of the results of experimental studies involving the effects of drugs and nervous stimulation. On the assumption that the secretory fibers to the sweat glands would undergo degeneration more promptly than the inhibitory fibers, he carried out the following experiment in cats. After stimulation of the sciatic nerve, following its division, no longer called forth the secretion of sweat on the hind paw, sweat secretion was elicited by means of pilocarpin, and the sciatic nerve was again stimulated. According to the results reported by Dieden, stimulation of the sciatic nerve, under these conditions, inhibited the secretion of sweat which had been brought about in the hind paw pad by the effect of pilocarpin. He concluded, therefore, that the sweat glands are innervated by inhibitory as well as secretory fibers. In another series of experiments reported by Dieden, the injection of adrenalin into the hind paw pad, after section of the sciatic nerve or only the dorsal roots of the lumbar nerves, was followed by a copious output of perspiration on the paw pad in question. This secretory activity ceased immediately upon stimulation of the dorsal roots of the

lumbar nerves. On the basis of this result, he concluded that the inhibitory fibers to the sweat glands are parasympathetic and traverse the dorsal nerve roots. As stated above, neither Langley (1922) nor Schilf and Mandur (1922) were able to confirm Dieden's findings regarding the effect of adrenalin on the secretion of sweat following nerve section. Neither do the results of their experiments support the theory that the sweat glands are supplied by inhibitory fibers. In the absence of experimental confirmation of Dieden's findings, it seems safer to assume that the sweat glands are supplied only by secretory fibers which are solely sympathetic.

THE MAMMARY GLANDS.

Anatomy.—The mammary gland derives its nerve supply through the lateral cutaneous rami of the second to the sixth intercostal nerves. The nipple and areola are abundantly supplied by efferent fibers which terminate in cutaneous end organs, and sympathetic fibers which supply the smooth muscle in the nipple and adjacent superficial area. The body of the gland is sparsely supplied by fibers which are mainly sympathetic. Sympathetic fibers reach the mammary gland through the fourth, fifth, and sixth intercostal nerves. The lateral cutaneous rami of these nerves give rise to glandular rami through which the sympathetic fibers are distributed throughout the gland. Sympathetic fibers also reach the mammary gland along the course of the long thoracic artery and the anterior perforating branches of the intercostal arteries which supply the gland. The sympathetic fibers within the mammary gland supply not only the blood vessels but also the smooth muscle which occurs sparsely distributed throughout the gland. Sympathetic fibers probably also terminate in relation to gland cells. Certain physiological data indicate the existence of secretory fibers in the mammary gland, but terminations of nerve fibers in relation to gland cells or within the acini of the gland have not been demonstrated anatomically. Neither have ganglion cells been observed in the mammary gland or in immediate proximity to it.

Nervous Influences in Mammary Function.—That nervous influences play a rôle in the functional activity of the mammary glands is well known, but the manner in which the output of mammary secretion is influenced by nervous impulses is not fully understood. The experimental studies carried out by the older investigators (Eckhardt, 1858; Röhrig, 1876; von Herff, 1889; Basch, 1893; Pfister, 1901) to determine the possible rôle of nervous influences in the secretory activity of the mammary glands yielded results which vary widely and afford no basis for definite positive conclusions. The results of all the experimental studies involving partial or complete denervation of the mammary glands indicate quite

clearly that the secretory function of these glands is in a large measure independent of nervous influences. Certain experimental data, however, strongly suggest that the mammary secretion may be influenced, at least qualitatively, through the nerves which supply the mammary gland. According to Pfister (1901), denervation of the mammary glands in the rabbit results in no quantitative changes in the production of milk. In Kahn's (1925) experiments, unilateral section of the nerves supplying the mammary gland in the guinea-pig resulted in a qualitative difference in the milk secreted by the glands on the two sides; the fat and casein content of the milk produced on the side of the operation was appreciably increased.

The development and growth of the mammary glands preceding puberty, their enlargement during gestation, the initiation of secretory activity, and the beginning of milk production following parturition are correlated with changes in the genital organs and are brought about largely through the stimulating influence of chemical substances (hormones) produced by the internal sex organs. Chemical stimuli and nutritive conditions also play a major rôle in milk production throughout the period of lactation. Nevertheless, nervous influences play an important rôle in the flow of milk or the facilitation of its extraction from the mammary gland. The stimulus afforded by the sucking of the young, in the human and animal species, is an important factor in increasing the output of milk at the beginning of lactation following parturition and in facilitating the extraction of milk throughout the lactating period. This stimulation of the nipple and areola elicits definite reflex reactions in the mammary glands which involve the movement of milk toward the outlet. These reactions in turn give rise to afferent impulses which result in more or less definite sensations.

The fact that unilateral stimulation of the nipple elicits reflex responses in both breasts indicates that the reflexes involved traverse the central nervous system. The afferent impulses are conveyed to the spinal cord through the afferent fibers supplying the nipple and areola; the efferent impulses reach the glands through visceral efferent and sympathetic neurons. The reflex reactions in question involve mainly the smooth muscles in the nipple and areolar area and the smooth muscle which occurs in small quantity throughout the gland. Whether stimulation of the nipple and areola affects the output of milk through direct secretory fibers is not known.

THE LACRIMAL GLANDS.

Anatomy.—The lacrimal gland derives its parasympathetic innervation from the sphenopalatine ganglion, and its sympathetic innervation from the superior cervical sympathetic ganglion. The

parasympathetic fibers traverse the maxillary nerve, its zygomatic ramus, the zygomatico-temporal branch of this ramus, and the lacrimal nerve with which the zygomatico-temporal forms an anastomosis. The sympathetic fibers traverse the internal carotid plexus and probably reach the lacrimal gland through the ophthalmic division of the trigeminal nerve and its lacrimal branch.

Secretory Function.—The secretory function of the parasympathetic nerves supplying the lacrimal gland has been demonstrated both clinically and experimentally. Section of the lacrimal nerve distal to the point at which the zygomatico-temporal nerve joins it abolished reflex lacrimation (Demtschenko, 1872). Goldzieher (1895) also pointed out that the functional activity of the lacrimal gland is disturbed immediately after paralysis of the facial nerve due to a lesion proximal to the geniculate ganglion. This observation was confirmed by Clapp (1897) and other more recent investigators. The preganglionic fibers involved in reflex secretory activity of the lacrimal gland are components of the facial nerve which reach the sphenopalatine ganglion through the greater superficial petrosal nerve (Müller and Dahl, 1910).

Stimulation of the cervical sympathetic also results in increased lacrimal secretion (Wolferz, 1870; Reich, 1873). Conversely, the lacrimal function is disturbed following cervical sympathetic paralysis. Whether the sympathetic fibers exert a direct secretory influence or affect the lacrimal function through vasomotor change is not definitely known. Müller and Dahl (1910) regarded the existence of sympathetic secretory fibers to the lacrimal gland as highly probable, although sympathetic fibers probably play no important rôle in reflex lacrimal activity.

THE GLANDS IN THE NASAL MUCOSA.

The mucous glands in the nasal and nasopharyngeal mucosa are supplied by both sympathetic and parasympathetic fibers through peripheral branches of the sphenopalatine ganglion. That the parasympathetic fibers exert a secretory influence on these glands is demonstrated by the fact that stimulation of the preganglionic components of the facial nerve results in acceleration of their secretory activity. They also react reflexly by increased secretory activity to afferent stimulation of the trigeminal nerve. The sympathetic fibers distributed to the nasal and nasopharyngeal mucosa probably are mainly vasoconstrictor fibers. The parasympathetic supply probably also includes vasodilator fibers.

THE SALIVARY GLANDS.

Anatomy.—The salivary system includes three relatively large glands, viz.: the parotid, submaxillary, and sublingual glands, with

ducts leading into the buccal cavity, and numerous small glands distributed throughout the buccal mucosa. These glands are innervated by both parasympathetic and sympathetic nerves. Their parasympathetic innervation is derived mainly through the facial and glossopharyngeal nerves and the otic and submaxillary ganglia. The sphenopalatine ganglion also plays a part in the innervation of the buccal mucosa. Their sympathetic innervation is derived from the superior cervical sympathetic ganglion through the internal and external carotid plexuses.

The parasympathetic fibers to the parotid gland are derived directly from the otic ganglion. They reach the gland through the auriculo-temporal nerve. The preganglionic fibers involved arise in the inferior salivatory nucleus, leave the brain stem as components of the glossopharyngeal nerve, traverse its tympanic ramus, and reach the otic ganglion through the lesser superficial petrosal nerve. The sympathetic fibers supplying the parotid gland are derived from the superior cervical ganglion through the internal carotid plexus.

The parasympathetic fibers to the submaxillary and sublingual glands are derived from the submaxillary ganglion and the ganglion cells which lie within the hilum of the submaxillary gland. The preganglionic fibers involved arise in the superior salivatory nucleus, pass out of the brain stem as components of the facial nerve, and reach the submaxillary ganglion through the chorda tympani which, in the distal part of its course, is incorporated in the lingual nerve. The sympathetic fibers supplying these glands are derived from the superior cervical ganglion through the external carotid plexus and the plexus on the external maxillary artery.

The ganglion cells in the submaxillary gland occur in small groups along the lobar and lobular ducts (Huber, 1896). These cells are essentially similar to the neurons in the submaxillary ganglion and may be regarded as part of that ganglion. Ganglion cells have not been observed in the sublingual gland. According to Langley (1890), the parasympathetic fibers supplying the submaxillary gland arise mainly from the ganglion cells lying within the hilum of the gland. The preganglionic fibers which terminate in relation to these cells are components of the chorda tympani which pass through the submaxillary ganglion. The parasympathetic fibers which supply the sublingual gland arise in the submaxillary ganglion.

The postganglionic fibers supplying the salivary glands are mainly unmyelinated fibers of small caliber. The majority of these fibers accompany the glandular ducts. Fiber bundles can be traced along the ducts into the lobules of the gland, where they form plexuses on the intralobular ducts. From these plexuses strands of two, three, or more fibers can be traced between the alveoli, where they give rise to perialveolar plexuses (Huber, 1896).

Retzius (1888) described plexuses of nerve fibers around the alveoli of the "small salivary glands" in the tongue of the rabbit. Cajal (1889) also described a plexiform arrangement of nerve fibers around the alveoli in the submaxillary gland of the rat and rabbit. Retzius was unable to determine whether the nerve fibers terminate on the outer surface of the membrana propria or in direct relation to the gland cells. According to Cajal, the ultimate fibrillæ termi-

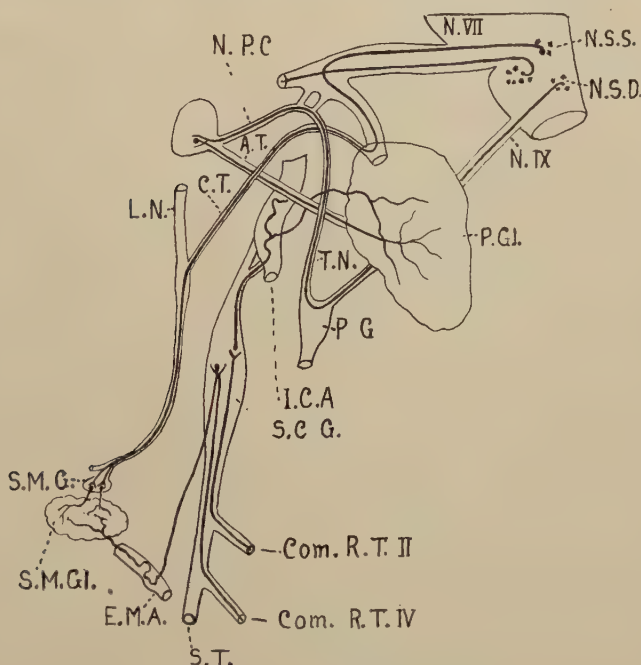


FIG. 48.—Diagram illustrating the innervation of the parotid and submaxillary glands. *A.T.*, auriculo-temporal nerve; *C.T.*, chorda tympani; *Com. R.T.II*, white communicating ramus of the second thoracic nerve; *Com. R.T.IV*, white communicating ramus of the fourth thoracic nerve; *E.M.A.*, external maxillary artery; *I.C.A.*, internal carotid artery; *L.N.*, lingual nerve; *N.VII*, facial nerve; *N.IX*, glossopharyngeal nerve; *N.P.C.*, nerve in the pterygoid canal; *N.S.D.*, inferior salivatory nucleus; *N.S.S.*, superior salivatory nucleus; *P.G.*, petrosal ganglion; *P.Gl.*, parotid gland; *S.C.G.*, superior cervical ganglion; *S.M.G.*, submaxillary gland; *S.M.Gl.*, submaxillary ganglion; *S.T.*, sympathetic trunk.

nate on the outer surface of the gland cells. According to Dogiel (1893), nerve fibers actually penetrate the membrana propria and terminate in direct relation to the gland cells. Berkley (1893) and Huber (1896) also expressed the opinion that the ultimate fibrillæ penetrate the membrana propria and terminate on the gland cells.

Secretory Activity of the Salivary Glands.—In general, the large salivary glands exhibit secretory activity only while food is being

eaten or in response to reflex or psychic stimulation. The small glands in the buccal mucosa secrete more or less continuously. In the ruminants, however, the large salivary glands, especially the parotid, exhibit some secretory activity while the animal is at rest, even in the absence of food in the mouth and in the absence of psychic stimulation. Scheunert and Trautman (1921) found that, in the sheep, the parotid gland produces a continuous flow of secretion, but the submaxillary gland exhibits secretory activity only while the animal is feeding. They observed no secretory output from the submaxillary gland in this animal during the intervals between feeding, even while cud chewing was in progress.

Evidence for the Existence of Secretory Fibers.—Ludwig demonstrated the existence of secretory fibers to a salivary gland as early as 1851. In his experiments, stimulation of the chorda tympani in the rabbit resulted in increased secretory activity of the submaxillary gland. Claude Bernard and Eckhard also maintained that the chorda tympani contains fibers which influence salivary secretion. That the glossopharyngeal nerve includes secretory fibers to the parotid gland was demonstrated by the work of Eckhard and Loeb (1870) and Heidenhain (1878). The weight of experimental evidence available at present favors the conclusion that the sympathetic supply to the salivary glands also includes true secretory fibers, especially to the submaxillary and sublingual glands. The parotid gland does not react to sympathetic stimulation by increased secretory activity in the dog. The parotid gland cells, however, exhibit characteristic histological changes following a period of sympathetic stimulation (Hitzker, 1914). Inasmuch as the secretory activity of the submaxillary and sublingual glands is augmented by both parasympathetic and sympathetic stimulation, these glands differ from other internal organs with respect to the effects of stimulation of these two sets of nerves. In this instance, the action of the parasympathetic and sympathetic nerves seems to be synergistic.

Specific Effects of Nervous Stimulation.—The secretory effects on the salivary glands of stimulating their parasympathetic and sympathetic nerves respectively differs somewhat in different animals. In the dog, according to the results of Heidenhain's (1878) classical experiments, the submaxillary and sublingual glands begin to secrete promptly when the chorda tympani is stimulated by weak induction shocks. By proper regulation of the stimulation this secretory activity may be kept up for hours. The secretion produced under these conditions is thin and watery and contains a very low percentage of solid matter. The flow of blood through the gland is increased and the organ assumes a redder color. The veins are also distended. If they are cut, the blood flows out rapidly and is redder than the blood in the resting gland. These facts

indicate dilatation of the small arteries and suggest that the parasympathetic nerves in question also contain vasodilator fibers. Stimulation of the sympathetic nerves supplying these glands brings about quite a different result. The meager secretion produced is thick and turbid and contains a high percentage of total solids. The gland also becomes pale. The veins are not distended. If they are cut, the blood flows out less rapidly and is darker than in the resting gland. These facts show that sympathetic stimulation also brings about vasoconstriction in these glands.

The results of Heidenhain's experiments showed clearly that sympathetic as well as parasympathetic stimulation augments salivary secretion. Vasomotor changes, however, constitute an important factor in such experiments. Doubtless, the abundant flow and watery character of the secretion produced during parasympathetic stimulation is determined largely by the increased blood supply to the glands. On the other hand, the meager flow and thick character of the secretion produced during sympathetic stimulation is correlated with a diminution in the blood supply by reason of vasoconstriction. These facts might suggest that the effects of nervous stimulation on salivary secretion are mainly manifestations of vasomotor phenomena, the rate of secretory activity depending only on the volume and pressure of the blood flowing through the glands. Ludwig was able to demonstrate, however, by the use of a mercury manometer, that stimulation of the chorda tympani for a certain length of time may result in secretory pressure in the submaxillary gland which greatly exceeds the intraglandular blood pressure. This shows that filtration from the blood is not the only factor involved in the secretory activity of the salivary glands. Furthermore, if the flow of blood be shut off completely from the submaxillary gland, stimulation of the chorda tympani still results in secretory activity for a short time. Stimulation of the chorda tympani, following the injection of atropin into the submaxillary gland, also results in vasodilatation but no secretory activity. This suggests that atropin paralyzes the secretory, but not the vasodilator fibers.

Simultaneous weak stimulation of the chorda tympani and cervical sympathetic brings about a greater increase in salivary secretion than the stimulation of either nerve separately (Langley, 1878). Simultaneous stimulation of these nerves by means of a strong stimulus, however, results in a lesser increase in secretion than stimulation of the chorda tympani alone (Czermak, 1857). This might be explained on the assumption that the sympathetic nerves, under certain conditions, exert an inhibitory influence on the salivary glands. That sympathetic stimulation may inhibit secretory activity of the submaxillary gland brought about by stimulation of the chorda tympani was observed by Czermak (1857). Mislowsky and Smirnow (1893) observed a similar inhibitory effect of sympathetic

stimulation on the secretory activity of the parotid gland brought about by stimulation of the auriculo-temporal nerve. That vasoconstriction due to sympathetic stimulation played an important rôle in these results seems highly probable. On the other hand, Langley (1889) was able to show that the secretory effect of sympathetic stimulation on the submaxillary gland is heightened by preceding stimulation of the chorda tympani for a short time. This result led him to conclude that parasympathetic stimulation increases the irritability of the gland cells. It also favors the assumption that the sympathetic nerves include true secretory fibers to the salivary glands.

By reason of the fact that both parasympathetic and sympathetic stimulation results in salivary secretion, even though the secretion produced during stimulation of the one differs from that produced during stimulation of the other of these two sets of nerves both quantitatively and qualitatively, Heidenhain advanced the theory that the same gland cells are innervated by both parasympathetic and sympathetic fibers. Inasmuch as stimulation of the chorda tympani called forth an abundant watery salivary secretion and stimulation of the cervical sympathetic a meager thick secretion, he concluded that the parasympathetic fibers to the salivary glands are essentially "secretory" and influence mainly the output of water and salts, while the sympathetic supply includes "trophic" fibers which influence mainly the output of organic substances. This conclusion, if correct, would have an important bearing on the functional relationship of sympathetic and parasympathetic innervation in general. The results of later investigations, however, do not justify the assumption that the parasympathetic and sympathetic nerves to the salivary glands exhibit such qualitative functional differences as Heidenhain was led to assume.

Knowledge of the specific distribution of the sympathetic and parasympathetic fibers, particularly in the submaxillary gland, and the specific changes brought about in the gland cells by sympathetic and parasympathetic stimulation respectively was advanced materially by the experimental histological studies of Hitzker (1914). According to his findings, the histological changes in the mucous cells brought about by stimulation of the chorda tympani and the cervical sympathetic are similar in character and indicate heightened secretory activity. On the other hand, the histological changes brought about in the serous cells are dissimilar. The effect on these cells of stimulation of the chorda tympani is manifested by enlargement and increased granulation of their cytoplasm. The effect of sympathetic stimulation is manifested by diminution in the size of these cells, decreased granulation of their cytoplasm and a less intense staining reaction of the nucleus. Simultaneous stimulation of the chorda tympani and the cervical sympathetic, accord-

ing to Hitzker, results in summation of the effects of both nerves on the mucous cells, but in interference of the sympathetic and parasympathetic influences with each other on the serous cells, resulting in enlargement of the cells due to parasympathetic, and decreased granulation of their cytoplasm due to sympathetic stimulation, and no change in the staining reaction of the nucleus. These facts strongly suggest that both the mucous and serous cells are innervated by both parasympathetic and sympathetic fibers. Although the effect on the mucous cells of stimulation of the chorda tympani for a given interval is more marked than that of stimulation of the cervical sympathetic for an equal interval, the impulses conveyed to these cells by parasympathetic and sympathetic fibers respectively must affect these cells in essentially the same manner. The effect of the parasympathetic and sympathetic fibers respectively on the serous cells must be regarded as antagonistic. These facts seem to warrant the conclusion that the impulses conveyed to the salivary glands by the parasympathetic and sympathetic fibers respectively differ qualitatively in their effect, particularly on the serous cells. Furthermore, the results of Babkin's (1913) experiments involving extirpation of the superior cervical sympathetic ganglion also suggest that impulses conveyed to the salivary glands by the same fibers may differ qualitatively in their effect on the gland cells. Nevertheless, vasomotor changes in the salivary glands effected by the nerves in question must always play an important rôle in determining the volume and character of the secretion produced.

Reflex Salivary Secretion.—The salivary glands react reflexly, not only to stimulation of the buccal mucosa, but also to strong stimulation of afferent nerves from other parts of the body, particularly the eyes, ears, and nasal mucosa. In general, the mere presence of water at ordinary temperatures or inert substances, *e. g.*, pebbles, in the mouth does not call forth a flow of saliva, but the salivary glands react more or less specifically to mechanical, chemical, and thermal stimulation of the buccal mucosa. On the basis of experimental studies, Haymann (1904) concluded that the buccal mucosa contains receptors which possess a high degree of specificity and that those which receive certain types of stimuli are not uniformly distributed. Consequently, the reflex response of the salivary glands varies with the kind of stimulation and the area of the buccal mucosa involved. This probably is an important factor in determining the quantitative and qualitative variations in the salivary secretion while different kinds of food are being eaten.

Strong afferent stimulation of a somatic nerve, *e. g.*, the sciatic, results not only in an increased output of saliva, but also in an increase in the organic constituents of the salivary secretion. Section of the cervical sympathetic trunk does not abolish reflex salivary

secretion, but results in qualitative changes in the saliva produced on the side of the operation. Section of the chorda tympani abolishes reflex secretory activity of the submaxillary and sublingual glands.

Paralytic Salivary Secretion.—Paralytic secretory activity is initiated in the submaxillary gland a short time after section of the chorda tympani (Bernard, 1864; Heidenhain, 1868; Langley, 1885; Bradford, 1888) and continues for two weeks or longer. A constant flow of thick secretion is produced during this time. Section of the parasympathetic fibers to the parotid gland is not followed by a similar paralytic secretion of this gland. Sympathetic stimulation during paralytic secretory activity of the submaxillary gland usually results in increased secretion. Section of the cervical sympathetic has no effect on paralytic secretion.

Dyspnea augments (Langley, 1885) and apnea inhibits paralytic salivary secretion. This led Langley (1898) to conclude that the gland cells which have become hyperirritable by reason of deprivation of their parasympathetic innervation react to the presence of carbon dioxide in the blood by paralytic secretory activity. The fact that such secretory activity usually ceases within three weeks after section of the nerve, however, militates against this conclusion. Unilateral section of the chorda tympani is also followed by increased secretory activity of the submaxillary gland of the opposite side. This was first observed by Heidenhain in the dog and later corroborated by Langley (1885) in the cat. As observed by Heidenhain, section of the nerve has no effect on this so-called antiparalytic salivary secretion. Consequently, this phenomenon cannot be associated with hyperirritability of the salivary center, as was suggested by Langley, but its real cause remains to be discovered.

Effects of Drugs on Salivary Secretion.—Intravenous injection of adrenalin brings about a marked increase in the production of saliva in the cat (Langley, 1901, 1902). The effect of adrenalin on salivary secretion is less marked in the dog and rabbit and absent in man (Bauer, 1912). Atropin in moderate doses abolishes the influence of the parasympathetic but not of the sympathetic nerves on salivary secretion. Ergotoxin abolishes the effect of the sympathetic but not that of the parasympathetic nerves on the submaxillary gland (Dale, 1906).

The data obtained from studies involving the effects of drugs on the activities of the salivary glands, like those obtained from other experimental studies, indicate that the salivary glands are innervated by both parasympathetic and sympathetic nerves and that both contain true secretory fibers. On the other hand, vasomotor phenomena must also be regarded as an important factor in the functional control of the salivary glands.

THE PANCREAS.

Extrinsic Nerves.—The pancreas derives its nerve supply from the celiac plexus mainly through the hepatic, superior mesenteric, and splenic plexuses. Offsets from the latter plexuses give rise to plexiform meshworks on the pancreatic vessels and enter the gland along with its blood supply. Isolated rami also enter the pancreas directly from the celiac plexus without traversing the plexuses on the pancreatic vessels.

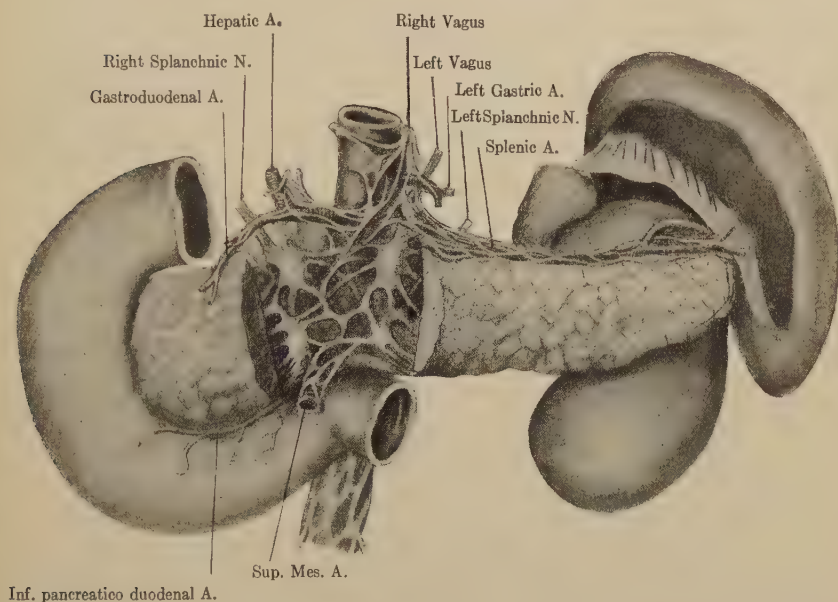


FIG. 49.—Diagrammatic illustration of the innervation of the pancreas. (Modified from Greving.)

The nerves supplying the pancreas are in part sympathetic and in part parasympathetic. Since both the splanchnic and vagus components involved traverse the celiac plexus, anatomical separation of the sympathetic and parasympathetic supply to the pancreas is impossible. The results of physiological experimentation, however, indicate clearly that the sympathetic and parasympathetic components are functionally distinct.

Intrinsic Nerves.—Certain of the older investigators, notably Cajal (1891) and E. Müller (1892), described elements in the parenchyma of the pancreas which they regarded as ganglion cells. Others, particularly Gentes (1902) and Pensa (1905), were unable to find ganglion cells in the pancreas. Ssobolew (1902, 1912) and more recently van Campenbout (1925, 1927) reported the existence

of ganglion cells in the pancreas. Ssobolew maintained that some of these cells undergo degeneration more rapidly than others following ligation of the pancreatic duct. He advanced the theory that the ganglion cells which undergo degeneration most rapidly, under these conditions, are functionally associated with the regulation of external pancreatic secretion, and those which persist longest, with the regulation of internal pancreatic secretion. This theory is not supported by the findings of later investigators.

The nerve fibers observed within the pancreas are mainly unmyelinated. As the nerves enter the pancreas they continue for some distance along the arteries, around which they form plexuses. Nerve fibers also deviate from the blood vessels at intervals and give rise to periacinar plexuses. Delicate fibers arising from these plexuses penetrate the *membrana propria* and terminate in slight bulb-like enlargements between the basal portions of the gland cells (Cajal, E. Müller). Similar plexuses also occur around the pancreatic islands. Fibers arising from these plexuses penetrate the islands and ramify among the insular cells, forming a plexiform meshwork and finally terminating in free endings between the cells. Both Gentes and Pensa emphasized the abundance of the nerve supply to the pancreatic islands as compared with the supply to the other parts of the pancreas.

That the postganglionic sympathetic fibers supplying the pancreas take origin in the celiac ganglia is generally conceded. The site of origin of the postganglionic parasympathetic fibers is not definitely known. If it can be assumed that ganglion cells are constantly present in the pancreas, it may also be assumed that these cells are the ganglionic components of the vagus efferent chains. Bugsch, Dresel, and Lewy (1921) assumed, mainly on the basis of Cajal's anatomical studies, that the preganglionic vagus fibers actually enter the pancreas and effect synaptic connections with ganglion cells located there. They also advanced the theory that some of the ganglion cells in the pancreas are parasympathetic, and others sympathetic. This theory is not supported by anatomical findings.

In view of our present knowledge regarding the location of the ganglionic neurons involved in the sympathetic and parasympathetic innervation respectively of other abdominal viscera, it seems highly improbable that preganglionic vagus fibers involved in the pancreatic supply make synaptic connections with neurons in the celiac ganglia. Hess and Pollak (1926) advanced certain data which they interpreted as indicating that ganglion cells involved in the parasympathetic supply to the pancreas are located in the vagus ganglia. They subjected dogs to extirpation of the pancreas and kept them alive for intervals up to three weeks by the administration of insulin as required. The celiac and vagus ganglia and the brain stem were

then examined for degenerative changes. Significant changes were found only in the vagus ganglia. Preparations of the jugular ganglion showed a high percentage, and preparations of the nodose ganglion a moderate percentage of the ganglion cells in an advanced stage of degeneration. They regarded these changes as the result of retrograde degeneration due to interruption of the axons by extirpation of the pancreas. Since no degenerative changes were found in the dorsal motor nucleus of the vagus, they concluded that the cells which underwent degeneration in the vagus ganglia represent parasympathetic ganglion cells. If this conclusion is confirmed by further investigation, the ganglionic components of the vagus efferent chains supplying the pancreas can be accounted for without the necessity of assuming the existence of ganglion cells in the parenchyma of the pancreas. The observation reported by certain investigators that multipolar neurons exist in the vagus ganglia will also assume greater significance. Nevertheless, if ganglion cells exist within the pancreas, it is highly probable that they are functionally incorporated in vagus efferent chains.

Afferent end organs in the form of Pacinian corpuscles have been described in the pancreas. According to Ssobolew (1902), these end organs are abundant in the pancreas of the cat. In a later study (1912), he also observed them in small numbers in the pancreas in man. In an investigation involving examination of the pancreas in man, Ceelen (1912) found Pacinian corpuscles in 89 out of 100 cases. According to his findings, they vary widely in number and distribution, being most numerous on the posterior aspect of the head, and less numerous in the body and tail of the pancreas. They occur not only in relation to the blood vessels and the serosa, but also in the parenchymatous tissue.

Nervous Regulation of Pancreatic Secretion.—Although the production of pancreatic juice is in a large measure determined by chemical stimuli (secretin), it has long been known that the external secretion of the pancreas is regulated in part by nervous influences. As early as 1873, Heidenhain and Landau observed that electrical stimulation of the medulla oblongata brings about an increase not only in the liquid, but also in the solid constituents of the pancreatic juice. They did not determine the path of the efferent impulses involved. Important contributions to the solution of this problem were made by Pavlov (1878) and his students. They observed early that the administration of atropin is followed by inhibition of pancreatic secretion. This suggested that the vagus innervation of the pancreas exerts an excitatory influence on its external secretory activity. The results of experimental studies carried out by Pavlov's students (Matt, 1894; Kudrewetsky, 1894; Modraskowski, 1906; Babkin and Sawitsch, 1908) all corroborate this theory. They demonstrated clearly that vagus stimulation augments the produc-

tion of pancreatic juice. Moreover, Kudrewetzky and Modrakowski were able to show that augmentation of pancreatic secretion may also be brought about by sympathetic stimulation, although the effect of sympathetic stimulation is much less marked than that of vagus stimulation. They also observed that the augmenting effect of sympathetic stimulation became more marked following vagus paralysis by means of atropin. Pavlov also pointed out that reflex inhibition of pancreatic secretion may be brought about by afferent stimulation of various peripheral nerves.

These experimental results require further explanation. In considering the effect of nervous stimulation on the production of pancreatic juice, the effect of the same stimuli on the production and flow of bile must not be disregarded. Vagus stimulation also results in increased production and flow of bile. According to Mellanby (1926), the introduction of bile of adequate reaction into the duodenum brings about an increased production of pancreatic juice by reason of the stimulating effect on the pancreas of secretion contained in the cells of the intestinal mucosa which is carried into the portal blood along with the bile salts contained in the liquid absorbed from the intestine. He also pointed out that neither paralysis of the vagi by means of atropin nor paralysis of the sympathetic nerves by means of ergotamin tends to diminish the capacity of bile in the intestine to act as a stimulus for the secretion of pancreatic juice. He also reported that the amount of pancreatic juice secreted following intravenous injection of secretin is independent of vagus paralysis by atropin. Analysis of the pancreatic juice secreted under the influence of secretin alone shows that the bicarbonate content remains constant, but the trypsinogen and amylase content steadily diminishes. Following vagus stimulation or the administration of pilocarpin, the bicarbonate concentration remained the same, but the trypsin and amylase contents of the pancreatic juice were increased. Mellanby concluded, therefore, that the production of pancreatic enzymes is subject to direct vagus control while the quantity of liquid secreted and its bicarbonate content is determined by secretin. According to this conception, the activities of the pancreas and liver, though not independent of nervous regulation, are interdependent on each other; the digestive functions of the former are correlated with the metabolic activities of the latter.

The internal secretory activity of the pancreas is also subject to regulatory nervous influences exerted mainly through the vagi. This theory, based mainly on the fact that the administration of pilocarpin in appropriate dosage brings about diminution of adrenalin glycosuria, was advanced by Eppinger, Falta, and Rudinger (1908). It was opposed by Frank and Isaak (1910) by reason of the fact that they were unable to bring about diminution of adrenalin

hyperglycemia by the administration of either cholin or pilocarpin. They concluded that the internal secretory activity of the pancreas is in no way subject to nervous control. As a result of more crucial experiments, de Corral (1918) showed clearly that vagus stimulation does result in increased internal secretion of the pancreas. He was able to bring about an unmistakable decrease in the sugar content of the blood by stimulation of the vagus below the cardiac branches in dogs in which the nerves supplying the liver had been destroyed by an operative procedure. The decrease in blood sugar occurred so promptly, in his experiments, that it could only be explained as the result of increased internal secretory activity of the pancreas brought about by the direct effect of vagus stimulation. Dogs which had been subjected to denervation of the liver by the operative procedure employed by de Corral, but not to vagus stimulation, regularly showed an increase in the sugar content of the blood which remained constant for a long time.

Many of the data obtained in more recent experimental studies carried out to determine the rôle of nervous influences in the regulation of the functional activities of the pancreas and liver also suggest that vagus stimulation augments the internal secretory activity of the pancreas. Whether the sympathetic innervation of the pancreas plays a rôle in its internal secretory activity is unknown.

THE SPLEEN.

Anatomy.—The nerve supply to the spleen involves the vagus and greater splanchnic nerves of both sides and the left phrenic nerve. The preganglionic splanchnic fibers supplying the spleen are components of the sixth, seventh, and eighth thoracic nerves (Schaefer and Moore, 1896). In the dog, according to Cleland and Tait (1927), the splenic venomotor fibers join the left phrenic nerve in the mid-cervical region. On the abdominal surface of the diaphragm they accompany the inferior phrenic artery for a short distance, and, deviating toward the celiac ganglion, join the plexus on the splenic vein. The splenic nerves arise mainly from the left celiac ganglion and accompany the splenic vessels on which they form a plexus (splenic plexus). Within the spleen, the nerves accompany the branches of the splenic artery and vein. Each nerve, like the vessel which it accompanies, supplies a circumscribed portion of the gland. There is, however, some overlapping of the terminal branches of adjacent nerves (v. Skramlik and Duran-Cao, 1925). According to Tait and Cashin (1925), the spleen is divided into a number of segmental zones which correspond to the ultimate branches of the splenic nerve. They also showed that these zones are at the same time nervous and arterial units. The venomotor nerves, according to Cleland and Tait (1927), are also distributed to

localized parts of the splenic veins. The splenic nerves are composed mainly of unmyelinated fibers arising mainly in the cœliac ganglia, but they also contain visceral afferent fibers. The afferent supply to the spleen seems to be especially abundant. The efferent fibers are distributed mainly to the splenic blood vessels and the smooth muscle in the splenic capsule and trabeculæ.

Effects of Sympathetic and Parasympathetic Stimulation.—

Inasmuch as the splenic capsule and trabeculæ contain smooth muscle fibers, contraction and relaxation of these fibers, with corresponding changes in the size and form of the spleen, in response to nervous stimulation, was to be expected. Many of the older investigators observed contraction of the spleen in response to stimulation of the greater splanchnic nerve, but observed no effect on the spleen on vagus stimulation.

Contraction of the spleen in response to sympathetic stimulation had been observed previously, but systematic studies of the effect of nervous stimulation were first undertaken by Bulgak (1877). In his experiments, stimulation of the greater splanchnic nerve, the cœliac ganglion, or the splenic nerves resulted in contraction of the spleen. The initial phase of this contraction was accompanied by blanching of the organ. This was followed by the appearance of lobulation and rounding off of the angles at the margins. Stimulation of the peripheral end of the cut vagus elicited no apparent reaction in the spleen, but stimulation of the central end of the vagus resulted in reflex splenic contraction. The vagus nerve seemed to exert no influence on the spleen. These findings were corroborated by those of Roy (1881), Schaefer and Moore (1896), and Magnus and Schaefer (1901). None of these investigators observed any reaction in the spleen to direct vagus stimulation. They concluded, therefore, that the spleen is innervated only by sympathetic nerves. Strasser and Wolf (1905) observed enlargement of the spleen following bilateral section of the greater splanchnic nerve, but did not ascribe this result to vagus influences.

Von Skramlik and Duran-Cao (1925) were able to demonstrate an inhibitory influence of vagus stimulation on the splenic musculature. In their experiments, stimulation of the greater splanchnic or splenic nerves in the dog resulted in contraction of the spleen accompanied by unequal blanching of its surface. If the stimulation continued, the blanching became uniform. The effect of stimulation reached its maximum in about thirty seconds. Following cessation of stimulation, the organ slowly resumed its previous condition. Stimulation of the vagus nerves produced no marked changes in the spleen, but, in many instances, the organ felt softer during vagus stimulation than before. Its tonus was appreciably diminished. Simultaneous vagus and splanchnic stimulation produced the same results as splanchnic stimulation alone, but stimula-

tion of the vagus immediately after the cessation of splanchnic stimulation hastened restoration of the spleen to the condition obtaining before splanchnic stimulation. In some instances, the time required for restoration following splanchnic stimulation was reduced by vagus stimulation to less than one-half the normal interval. In these experiments, the effect of vagus stimulation while the spleen was in a state of contraction, following cessation of splanchnic stimulation, was unmistakable. These results strongly suggest that the vagus fibers exert an inhibitory influence on the smooth muscle fibers in the splenic capsule and trabeculae. Physiological dilatation of the spleen probably is brought about mainly by impulses mediated through the venomotor fibers. In the experiments of Cleland and Tait (1927), electrical stimulation of these fibers resulted in engorgement of the spleen corresponding in degree and in duration to the contraction of the splenic vein. Section of these fibers abolished reflex dilatation, and the spleen remained in a state of partial contraction following degeneration of these fibers. They concluded, on the basis of these results, that the venomotor fibers constitute the efferent pathway for physiological splenic dilatation.

THE THYROID GLAND.

Anatomy.—The thyroid gland derives its nerve supply mainly from the cervical sympathetic, but also receives vagus fibers (Renner, 1924). The sympathetic supply is derived mainly from the middle cervical ganglion. In the absence of this ganglion, the rami which supply the thyroid arise directly from the cervical sympathetic trunk. In some instances, fibers arising in the superior cervical ganglion also reach the thyroid gland (Sinakewitsch, 1908). The majority of the nerve fibers supplying the thyroid traverse the superior and inferior laryngeal nerves and join the thyroid arteries on which they form the superior and inferior thyroid plexuses. The great majority of the nerve fibers which enter the thyroid gland are unmyelinated. The older investigators, particularly Kölliker (1855), Peremeschko (1867), and Zeisz (1877), observed that the nerve fibers within the thyroid gland in general accompany the blood vessels; therefore, they regarded them as vasomotor in function. The majority of the more recent investigators who studied the distribution of these fibers supported the theory that they terminate both in relation to the thyroid follicles and in the walls of the blood vessels. Ganglion cells have not been observed in the thyroid gland by any of the more recent investigators.

Nervous Influences in the Regulation of Thyroid Function.—Poincare (1875) advanced the theory that the nerves to the thyroid gland include both secretory and vasomotor fibers, although experimental data in support of such a theory were not at hand. Wysz

(1889) and Anderson (1894) observed that the thyroid gland cells undergo morphological changes following the administration of pilocarpin which are comparable to the morphological changes exhibited by the salivary gland cells during secretory activity. Inasmuch as pilocarpin stimulates salivary secretion by reason of its effect on the peripheral terminations of the secretory nerves, they concluded that the nerves supplying the thyroid gland also subserve a secretory function. Schaefer (1909) also observed increased thyroid secretory activity following the administration of pilocarpin. Schmidt (1896) was unable to corroborate their findings. In his experiments, the injection of pilocarpin resulted in copious salivation, but he could detect no changes in the secretory activity of the thyroid gland. Neither could Huerthle (1894) observe changes in the thyroid gland cells microscopically following electrical stimulation of the laryngeal nerves. He concluded that nervous stimulation has no effect on the secretory activity of the thyroid gland. On the contrary, Chrisafulli (1892) and Trautmann (1895), on the basis of their experimental results, supported the theory that the nerve supply to the thyroid gland includes both secretory and vasomotor fibers. Katzenstein (1897) reported profound degenerative changes in the glandular tissue following denervation of the thyroid. Luebecke (1902) could not confirm this finding. He observed no degenerative changes in the thyroid gland following section of the laryngeal nerves.

Other investigators gave special attention to the vasomotor innervation of the thyroid gland. Briau (1898) reported marked vasomotor changes in the thyroid in response to sympathetic stimulation, but observed no other changes in the gland resulting from such stimulation. Cyon (1898) observed a marked drop in blood pressure in the thyroid and a corresponding change in the size and turgor of the gland as a result of stimulation of the superior thyroid nerve. The blood vessels were markedly dilated and the flow of blood from a severed vein was appreciably increased during the nervous stimulation. He was able to determine, by further experimentation, that the superior laryngeal nerve contains both vasodilator and vasoconstrictor fibers for the thyroid, but the former predominate in this nerve. On the other hand, vasoconstrictor fibers predominate in the thyroid supply derived through the inferior laryngeal nerve. In some instances, vasodilator fibers also predominate in this nerve. Sinakewitsch (1908) concluded, on the basis of experimental data, that both the superior and inferior laryngeal nerves convey both vasoconstrictor and vasodilator fibers to the thyroid, and that in some instances the vasodilator; in others, the vasoconstrictor fibers predominate in the superior laryngeal nerve. The vasoconstrictor fibers commonly predominate in the inferior laryngeal supply to the thyroid.

In an investigation undertaken to determine the possible direct nervous influence on the secretory activity of the thyroid gland, Wiener (1909) cut the various nerves to the thyroid on one side, and later compared the lateral halves of the gland with respect to weight and thyroglobulin content. In his experiments, section of the vagus or extirpation of the superior cervical sympathetic ganglion brought about no apparent changes in the gland or in its thyroglobulin content. Extirpation of the inferior cervical sympathetic ganglion was followed by diminution in the size of the gland on the side of the operation and a decrease in its thyroglobulin content. He concluded, therefore, that the sympathetic innervation of the thyroid gland exerts both trophic and secretory influences.

The existence of true secretory fibers in the nerves supplying the thyroid was also assumed by Asher and Flack (1911). This assumption was based mainly on the fact that stimulation of the laryngeal nerves brings about the same heightened excitability of the depressor nerve and increased effect of adrenalin on blood pressure as is brought about by the intravenous injection of thyroid preparations. Asher and v. Rodt (1912) also observed that the excitability of the splanchnic nerves is heightened during stimulation of the nerves to the thyroid gland.

In a further experimental study carried out under Asher's direction, Ossokin (1914) corroborated the findings of the earlier investigators who maintained that the laryngeal nerves convey both vasodilator and vasoconstrictor fibers to the thyroid gland. He demonstrated the existence of vasomotor fibers in the branches of the superior and inferior pharyngeal nerves which reach the thyroid. He also showed that vagus excitability is increased during stimulation of the nerves to the thyroid. Consequently, the increased output of thyroid secretion due to nervous stimulation seems to exert an influence on both parasympathetic and sympathetic nerve terminations. More recently, Asher and Pfüger (1927) reported the results of experiments which seem to indicate that sympathetic denervation of the thyroid results in diminution of the capacity of the body tissues, particularly the subcutaneous connective tissue and muscles, for absorption. On the basis of their experimental findings, they concluded that at least some of the normal functions of the thyroid depend on its sympathetic innervation.

The experimental data at hand demonstrate clearly the existence of vasodilator and vasoconstrictor fibers in the nerves supplying the thyroid gland. Vasomotor changes probably play an important rôle in the secretory activity of this gland. On the other hand, the experimental data which have led various investigators to conclude that the thyroid gland also receives direct secretory impulses through its nerve supply cannot be disregarded. The exact rôle of the

secretory fibers in the functional regulation of the thyroid under normal conditions, but more especially under conditions of hypo- and hyperthyroidism awaits further investigation.

THE ADRENAL GLANDS.

Extrinsic Nerves.—The adrenal gland receives an abundant nerve supply through the adrenal plexus. This plexus is derived mainly from the celiac plexus, but is connected with the phrenic plexus above and the renal plexus below. It also includes direct fibers from the greater splanchnic and a smaller number from the vagus and phrenic nerves. The great majority of the fibers in the adrenal plexus are myelinated, but lose their myelin sheaths on passing into the small ganglia which are situated in the adrenal medulla or just within the connective tissue capsule of the gland.

Intrinsic Nerves.—As the nerves enter the adrenal gland from the adrenal plexus, some are distributed to the capsule and cortical portion of the gland, but most of them enter the adrenal medulla. The intrinsic nerves are composed of both myelinated and unmyelinated fibers. Myelinated fibers are most numerous in the nerves which are distributed to the capsule and superficial portions of the gland. Relatively few myelinated fibers occur in the medulla.

Dogiel (1894) recognized a plexiform meshwork of nerves in the adrenal capsule, another in the cortex, and a third in the medullary portion of the gland. Renner (1924) also recognized these three plexuses. The outer plexus supplies the capsule and gives off numerous branches to the adrenal cortex. The nerves which constitute the cortical plexus give rise to networks about cortical cell groups, without penetrating between the cells of the groups. Many of the fibers terminate in relation to cortical cells (Renner, 1925). The adrenal medulla contains numerous small ganglia and an abundant supply of nerve fibers, many of which terminate in relation to chromaffin cells. The ganglion cells in these ganglia are morphologically similar to those in other parts of the autonomic nervous system. In general, the cell body is enclosed in a capsule, but occasional individual ganglion cells which exhibit no cell capsule occur among the chromaffin cells in the medulla. Cells of the latter type, through their processes, seem to sustain an intimate relationship to the chromaffin cells (Renner).

The significance of so large a number of ganglion cells in the adrenal medulla is not known. Their existence there probably is to be explained on the basis of the sympathetic origin of the chromaffin cells. Having been displaced into the adrenal body, possibly some of the embryonic cells of nervous origin, under the influence of the adrenal cortex, develop into chromaffin cells, and others, under nervous influence, become differentiated into ganglion cells.

On the other hand, it may well be that, in the displacement of the cells which give rise to the adrenal medulla from the sympathetic primordia, neuroblasts become displaced into the adrenal body with the cells which are destined to become differentiated into chromaffin cells.

Nervous Regulation of Adrenal Function.—Although the cortical portion of the adrenal glands seems to be essential to life (Crowe and Wislocki, 1914), little is known regarding its specific functions. That the production of adrenalin is increased by stimulation of the splanchnic nerves was first maintained by Dreyer (1899). Tscheboksaroff (1910) and Asher (1912) also reported increased secretion of adrenalin during stimulation of the splanchnic nerves independent of any change in the flow of blood through the adrenal gland. Certain data advanced by Stewart and Rogoff (1919) also indicate the existence of secretory fibers to the adrenals. On the contrary, Popielski (1918) could demonstrate no increase in the adrenalin output in the dog due to splanchnic stimulation. Section of the splanchnic nerves results in diminution of the adrenalin output. According to Tscheboksaroff, a rise in blood pressure brought about by stimulation of a sensory nerve exerts no noticeable influence on the adrenalin output. According to Gley and Quinquad (1921), the effect of splanchnic stimulation on blood pressure is manifested in two phases. Splanchnic stimulation brings about an immediate rise in blood pressure by reason of its direct vasomotor effect. This represents the first phase. The second phase is initiated a little later by reason of the effect of an increased discharge of adrenalin into the blood. This finding was corroborated by the experimental results obtained by Tournade and Chabrol (1919). In their experiments, an anastomosis was effected between the adrenal vein of a large dog and the jugular vein of a smaller one. Thus the adrenalin produced by the gland of the large dog was introduced into the blood of the smaller one. On stimulation of the peripheral end of the splanchnic nerve of a large dog, blood pressure rose immediately in this animal and a little later in the smaller one. Inasmuch as the increased output of adrenalin due to splanchnic stimulation could not change the adrenalin content of the blood of the first animal, this result proves conclusively that the rise in blood pressure in this animal was due to the direct vasomotor effect of splanchnic stimulation. The rise in blood pressure which followed in the second animal was due to the increased adrenalin content of the blood flowing into its jugular vein from the adrenal vein of the first, brought about by splanchnic stimulation. This represents the second phase in the effect of splanchnic stimulation on blood pressure, and proves conclusively that the output of adrenalin is increased on sympathetic stimulation of the adrenal gland.

Although the anatomical data available indicate clearly that the

nerve supply to the adrenal gland includes parasympathetic fibers, little is known regarding the rôle of the parasympathetic nerves in the regulation of adrenal function. The sympathetic supply to the adrenals includes vasodilator fibers. Sympathetic stimulation through the splanchnic nerves commonly results in adrenal hyperemia and an increased outflow of blood from the gland. Although splanchnic stimulation does not elicit vasoconstriction in the adrenals, it has been assumed by certain physiologists, by reason of the fact that adrenalin produced vasoconstriction in the adrenal gland, that the sympathetic supply to this gland also includes vasoconstrictor fibers.

The secretory activity of the adrenals may be influenced reflexly by stimulation of afferent nerves from various parts of the body. It is also subject to impulses emanating from the central nervous system. Afferent nervous stimulation, psychic disturbances, or direct injury to the brain may exhaust the adrenalin supply. Section of the splanchnic nerves, however, prevents this result. It is highly probable that there is a center in the medulla oblongata through which the production of adrenalin is regulated. The center in question also exerts an influence on the sugar content of the blood. Puncture of the floor of the fourth ventricle which brings about hyperglycemia also affects adrenal secretion. Indeed, the changes in the sugar content of the blood are in part referable to the effect of modified adrenal activity.

The adrenal glands occupy a peculiar position among the endocrin organs with respect to their functional relationship to the nervous system. This is indicated both by the marked effect of sympathetic stimulation on adrenal activity and the retardation of adrenal secretion following section of the splanchnic nerves. The fact that adrenal insufficiency (Addison's disease) is but slightly affected by organotherapy probably is correlated with the peculiar functional relationship of these glands to the autonomic nervous system.

CHAPTER XII.

INNERVATION OF THE URINARY ORGANS.

THE KIDNEY.

Extrinsic Nerves.—The nerve supply of the kidney is derived directly from the renal plexus which extends from the aortic plexus along the renal artery to the hilum of the kidney. It is made up mainly of branches from the celiac ganglion and fibers from the aortic plexus. It is also joined by the lowest splanchnic nerve and communicating branches from the adrenal plexus. In some instances, at least one branch of the lesser splanchnic nerve also joins the renal plexus. According to Langley and Anderson (1896) and Jost (1914), the renal plexus is also joined by one or more slender rami from the lumbar portion of the sympathetic trunk. Vagus branches run directly to the renal plexus in many, but not in all cases. Direct vagus branches seem to occur more commonly on the right than on the left side (Renner, 1924). The majority of the vagus fibers involved in the renal supply traverse the celiac ganglion. Preganglionic fibers supplying the kidney are present in all the splanchnic nerves. Clinical evidence seems to indicate that the afferent fibers supplying the kidney are derived mainly from the tenth, eleventh, and twelfth thoracic nerves.

The renal plexus shows a wide range of variation in the configuration of the nerve fiber bundles which compose it and in the distribution of its ganglia. In cases in which the ganglion cells in the celiac plexus are not all incorporated in one or two ganglia, there is not uncommonly a ganglion in the renal plexus near the origin of the renal artery. This may be regarded as the first renal ganglion. The renal plexus usually comprises one or more additional ganglia located nearer the hilum of the kidney. These ganglia usually occur at nodal points in the plexus. Renner (1924) also found ganglion cells either singly or in very small groups in preparations of the renal plexus at points where no ganglionic enlargement was apparent. Such cells may occur at a nodal point or in the course of a fiber bundle.

According to Renner, the ganglion cells in the renal plexus are in general similar to those in other abdominal ganglia. He described them as rounded or oval cells with numerous processes which could usually be traced for some distance. Occasionally the axon of one of these cells could be traced into a fiber bundle in the plexus. In

general, the dendrites penetrate the cell capsule. Renner found no ganglion cells within the renal parenchyma.

Intrinsic Nerves.—The nerves which enter the kidney from the renal plexus accompany the renal artery and its branches around which they form plexuses. Even after the arteries enter the renal parenchyma, nerve fiber bundles may still be observed macroscopically along their walls. The intrinsic nerve plexuses commonly divide at the bifurcation of the arteries and continue even along the smaller arterial branches. In favorable microscopic preparations nerve fibers may be observed in relation to arterioles and capillaries. Afferent nerve fiber terminations have also been described in the kidney, especially in the musculature of the renal pelvis, the adventitia and media of the renal vessels, and the renal capsule (Renner, 1924).

The nerve fibers in the parenchyma of the kidney are mainly unmyelinated fibers of small caliber. Renner (1924) observed very few small myelinated nerve fibers in the renal parenchyma, although myelinated fibers occur in greater abundance in the region of the renal calyces and in the renal pelvis. According to Habler (1922), the renal calyces are richly supplied with unmyelinated nerve fibers which terminate in relation to the musculature, including the smooth muscle fibers which he claimed to have observed in the renal calyces above the sphincter papillæ.

Nervous Influence on Renal Functions.—Function of the Renal Nerves.—According to not a few investigators, including Cushny (1917), Millikan and Karr (1925), and Gubergritz and Itschenko (1926), the function of the renal nerves is essentially vasomotor. They regard the splanchnic supply to the kidney as including many vasoconstrictor and few vasodilator fibers, but no secretory fibers. Since splanchnic stimulation results in constriction of the renal blood vessels with diminution of the volume of blood flowing through the kidney and diminution in the output of urine, and section of the splanchnic nerves results in dilatation of the renal blood vessels with increased output of urine, it seems unnecessary to assume the existence of renal secretory fibers in the splanchnic nerves. Neither is the evidence which seems to support the theory that the vagus nerves convey secretory fibers to the kidneys regarded as conclusive by all investigators.

The experimental data available at present indicate clearly that denervation of the kidneys is not incompatible with life. It has been shown experimentally that excretion may continue many months, perhaps indefinitely, after all connections of the kidney with the central nervous system have been divided. Claude Bernard (1859) showed that secretion of urine by the affected kidney is increased following unilateral section of the splanchnic nerves in the dog. This was confirmed by the work of Eckhard (1869),

Grek (1912), Rhode and Ellinger (1913), Jungmann and Meyer (1913), and not a few later investigators. Carrel and Guthrie (1906) transplanted the kidneys of one dog into another and kept the latter alive for many days after removal of its own kidneys. Clearly, the kidney function was, in this case, carried out in the absence of direct nervous influences.

The first detailed study of the function of the kidney after transposition was carried out by Lobenhoffer (1913). In his experiments, the pedicle was severed and the kidney was transposed to the splenic vessels. On the basis of his results, he concluded that a kidney transposed in this manner is able to meet the ordinary demands of life. Zaaier (1914) reported the case of a dog which lived six years following transposition of its single kidney to the iliac vessels. Dederer (1918) transposed the left kidney of a dog to the vessels of the neck, and two weeks later removed the right kidney. The dog remained alive and well for more than four months after removal of the right kidney. Phenolsulphonephthalein was excreted rapidly by the transposed kidney and its output of urine was markedly increased following removal of the other kidney. In another experiment, Dederer (1920) homotransplanted a kidney and an ovary from one dog to another of the same litter. The dog with the transplanted kidney died of distemper twenty-six days later. Examination of the transplanted kidney showed that it reacted to the severe constitutional infection, distemper, in a manner similar to that of the animal's own organs. In this case, the transplanted kidney could have had no nervous connections, yet, although the animal had two kidneys of its own, phenolsulphonephthalein appeared in the urine of the transplanted kidney two minutes and forty seconds after its intravenous injection.

Quinby (1916) reported the results of a large number of experiments carried out on dogs in which the kidney on one side was removed and then reimplanted by anastomosing the severed vessels and ureter. According to Quinby, stripping of the renal vessels of nerve fibers is not sufficient to insure complete denervation of the kidneys because a few nerve fibers are actually within the vessel walls. In one series of animals, the ureters were brought out through the flanks two days to three weeks after the primary operation, and the urines were collected and compared. In this series, the output of both liquid and salt was increased, and this increase persisted ten to fourteen days. On the normal side, the flow of urine was temporarily inhibited by handling the ureter. Such temporary inhibition was not apparent on the opposite side, but urine flowed from the denervated kidney as soon as the ureter was opened. In another series of animals, the normal kidney was removed five days to two weeks after the primary operation. The capacity of the single denervated kidney to eliminate following

intravenous injection of normal salt solution, lactose solution and phenolsulphonephthalein was compared to that of a normal dog which had been subjected to unilateral nephrectomy. In a third series of animals, *Quinby* (1917) tested the response of the denervated kidney to intravenous injection of hypertonic solutions of sodium chloride, urea, and caffeine, and found that the reactions of the normal and the denervated kidney to these solutions were practically identical. These findings strongly suggest the absence of secretory fibers to the kidney.

In *Bellido's* (1917) experiments, denervation of one kidney by cutting all the nerves along the renal vessels resulted in moderate polyuria from that side which was still further increased by injection of a saline solution. When he injected blood from a uremic animal, as a specific chemical stimulus, the denervated kidney responded in the same way as the intact organ. Yet, *Bellido* reported that when both kidneys were denervated, there was polyuria for as long as two weeks; then suppression, and the animals died in coma. On the other hand, *Boeminghaus* (1923) reported that six animals in which he had denervated both kidneys by tearing away all the fibers of the renal plexus and painting the hilum and pedicle of the kidney with a concentrated solution of phenol lived until they were killed for autopsy nine months later.

Marshall and Kolls (1919-1920), who made a most painstaking study of the results of denervation of the kidney in relation to diuresis and urinary secretion, agreed with *Quinby*, that depriving a kidney of its nerve supply results in an increased output of urine on that side with a relative lowering, but total increase of solids. They found that the increased excretion of urine by the denervated kidney persisted for months after the operation, whereas *Quinby* had reported that it persisted for only ten days to two weeks. On the basis of their experimental results, they concluded that the changes noted in the secretory activity of the denervated kidney were due solely to vasodilatation with the consequent increased flow of blood through the kidney. When the renal artery was constricted by artificial means after denervation of the kidney, the output of urine was correspondingly reduced. They also found that when the denervated kidney was secreting much more urine than the normal kidney, the normal ratio could be reestablished by paralyzing the splanchnic on the normal side. The results of their experiments lend no support to the theory that secretory nerves play any part in the regulation of renal secretion.

The results obtained by *Milliken and Karr* (1925) in general corroborate those of *Marshall and Kolls*. They also afford additional evidence that denervation of both kidneys, in experimental animals (dogs), as far as this is possible by cutting all the visible fibers of the renal plexus, produces no untoward results, and that

the animal may continue to live in good health for an indefinite period. Neither did Gubergritz and Itschenko (1926) find any positive evidence in support of the theory that renal secretory activity is regulated either in whole or in part by secretory fibers.

The fact that denervation of both kidneys is not incompatible with life and that, as pointed out by Millikan and Karr, the denervated kidneys are able to withstand exigencies more rigorous than are likely to occur under ordinary conditions of life, do not prove the absence of secretory fibers to the kidney. Furthermore, experimental data are not wanting which have been interpreted as indicating that true secretory fibers play an important rôle in the nervous regulation of renal secretion.

In a series of experiments carried out by Asher and Pearce (1913), the entire renal nerve supply on one side was anesthetized by the local application of a concentrated solution of phenol. The splanchnic nerves on the opposite side were divided. Following decerebration of the animal, the vagus on this side was subjected to intrathoracic stimulation for varying periods. During these periods, the quantity of urine secreted by the kidney in question was increased, while that secreted by the other kidney remained unchanged. Furthermore, the urine secreted under vagus stimulation differed from that secreted by the other kidney during the same period. Its solid contents were markedly increased. They concluded, therefore, that vagus stimulation exerts a true secretory effect on the kidney. These findings were in general corroborated by those of Mauerhofer (1913), but the results of later experiments carried out by Pearce and Carter (1915) did not fully confirm the earlier results reported by Asher and Pearce.

Following section of the vagus nerves, Jungmann and Meyer (1913) observed diminution in both the quantity of urine secreted and its solid constituents. Occasionally, however, they observed an increase in the output of urine. This suggested to them that the vagus may, under certain conditions, also exert an inhibitory influence on renal secretion. According to Ellinger (1921), the vagus supply to the kidney includes fibers which augment diuresis without increasing the quantity of urine. Nakazawa (1924) observed an increase in the nitrogenous constituents of the urine following vagus section. On the basis of this finding, he concluded that the vagus includes fibers which inhibit the nitrogen output.

Rohde and Ellinger (1913) and Jost (1914) suggested that the splanchnic nerves also convey fibers which exert a direct secretory influence on the kidney. Ellinger (1921) later maintained that the splanchnic fibers accompanying the renal artery exert an inhibitory influence on the excretion of both water and the solid constituents of the urine. He maintained that the effect of the vagus and splanchnic nerves is the same on the excretion of water, but opposite on

the excretion of the solid constituents of the urine. According to Ellinger and Hirt (1925), the greater splanchnic nerve augments, while the fibers leaving the sympathetic trunk in the lower thoracic and lumbar segments inhibit the output of ammonia. The lower fibers also inhibit the output of phosphates but augment slightly the total nitrogenous output. On the other hand, the greater splanchnic nerve inhibits the total nitrogenous output, but augments the output of phosphates. They also pointed out that the vagus and splanchnics are mutually antagonistic in their effect on diuresis. When the lesser splanchnic was divided before section of the vagus, in their experiments, the output of urine following vagus section was greatly increased by reason of the absence of vasoconstriction. On the other hand, when vagus section was carried out first, the output of urine following section of the lesser splanchnic was also greatly augmented. These results were due in a large measure to vascular changes, but, as demonstrated by Asher (1915) and his students, the vagus supply to the kidney includes no vasomotor fibers, nor does vagus stimulation result in renal vasodilatation.

These experimental results strongly suggest that renal secretory activity is influenced to some extent by nervous impulses acting directly on the kidney cells. The output of both water and the solid constituents of the urine is, however, determined in so large a measure by the volume of blood flowing through the kidney that the exact rôle of secretory nerves, if the kidney is supplied by secretory fibers, is not easily determined. In view of the fact that denervation of both kidneys, in experimental animals, is not necessarily followed by untoward results, and in view of the volume of experimental data which seems to indicate that the renal output is determined solely by the volume and content of the blood flowing through the kidney, the burden of proof must still rest with those who maintain that the kidney is supplied by true secretory fibers.

Reflex Regulation of Renal Function.—That the secretory activity of the kidney is subject in some degree to reflex nervous influences is well known. Cooling of the skin results in inhibition, while increasing the cutaneous temperature results in augmentation of renal secretion. This is probably due mainly to vasomotor changes in the kidney. Cold applications to the skin of an experimental animal results in appreciable decrease in the size of the kidney and diminution of pressure in the renal vein. Similar reduction in the size of the kidney may also be brought about by afferent stimulation of a peripheral nerve, *e. g.*, the sciatic or an intercostal nerve.

Renal activity is also subject to reflex inhibition elicited by impulses arising in the ureter. Renal colic is not uncommonly accompanied by anuria which may persist for hours or even days. This probably is the result of reflex spasm of the renal arteries. The same result may also be brought about by kinking or compres-

sion of the ureter. Pflaumer (1919) was unable to elicit any effect on renal secretion by mechanical stimulation of the mucosa of the ureter. On the other hand, he observed inhibition of renal secretion as the internal pressure of the urinary bladder became increasingly greater (vesico-renal reflex). Ureteral stasis also inhibits the output of urine (uretero-renal reflex).

Central Nervous Influences on Renal Function.—That impulses of central nervous origin influence renal secretion is well known. Claude Bernard observed polyuria following a lesion in the floor of the fourth ventricle between the vagus and vestibular nuclei. Meyer and Jungmann (1913) produced a lesion in the floor of the fourth ventricle which resulted in an increase in the output of urine, but in a proportionately greater increase in the sodium chloride output which did not, however, affect the salt content of the blood, even though the animal had previously been rendered salt-poor. This result of the lesion was not observed following section of the splanchnic nerves. Obviously, the efferent impulses involved are carried out over these nerves. According to Jungmann (1922), puncture of the sugar center in the medulla results in diuresis with increased elimination of sodium chloride, independently of its effect on the sugar content of the blood.

The above results probably could be explained on the assumption that a lesion in the region of the sugar center involves fiber tracts which mediate impulses which are conveyed via the splanchnic nerves to the kidney as well as to the liver. Dresel (1922) presented evidence which he interpreted as indicating that the effects on renal secretion of lesions in the medulla are not the results of injuries to fiber tracts, but to medullary centers. In collaboration with Brugsch and Lewy, he found a region medial to the spinal tract of the trigeminal nerve, ventromedial to the restiform body, and dorsal to the nucleus of the facial nerve which he regarded as the center which regulates both the elimination of water and sodium chloride. That lesions of the diencephalic autonomic center result in disturbances of renal function is also well known.

Renal secretory activity is also subject to psychic influences. Not uncommonly polyuria occurs as an accompaniment of epileptic seizures and violent attacks of migraine. It may also accompany certain psychic states, *e. g.*, expectancy or fright. Doubtless, the impulses involved in these conditions are mediated through the diencephalic autonomic center and the efferent pathways leading from these centers to the cells of origin of the splanchnic nerves.

Although nervous influences play an important rôle in renal secretion, this rôle must be regarded as only regulatory. Furthermore, it is dependent, in a large measure, on the vasomotor control of the renal blood vessels exerted through the sympathetic nerves. Renal function is determined mainly by the inherent capacity of

the renal elements, the hydrostatic relationship of the blood to the kidney, and the stimuli to the renal secretory elements afforded by substances in the circulating blood.

THE URETER.

Nerve Supply.—The ureter derives its nerve supply mainly from the renal, spermatic (or ovarian), and hypogastric plexuses. A subordinate plexus derived from the vesical plexus also surrounds its lower portion. The afferent fibers supplying the ureter are mainly components of the eleventh and twelfth thoracic and first lumbar nerves. Afferent fibers probably are also included in the vagus supply to the ureter.

The arrangement of the nerves in the wall of the ureter seems to be relatively simple. The majority of the fiber bundles run longitudinally, but branch freely and intercommunicate with each other. In man and certain other mammals, particularly dogs and cats, groups of ganglion cells are associated with the intrinsic nerves in the lower third of the ureter. According to Hryntschak (1925), ganglion cells are absent in the ureter of the pig. Ganglion cells have not been observed in the upper two-thirds of the ureter in any animal. The sympathetic and parasympathetic components of the nerve supply to the ureter cannot be differentiated anatomically. It is highly probable, however, that the ganglion cells in the lower third of the ureter are incorporated in vagus efferent chains. The majority of the intrinsic nerve fibers are unmyelinated and of small caliber.

Nervous Control of the Ureteral Musculature.—The ureter is a relatively thick-walled muscular tube through which the renal secretion is conveyed to the urinary bladder. It is abundantly supplied by nerves both of sympathetic and parasympathetic origin, but the rôle of these nerves in the functional activity of the ureter is little understood. Like other smooth muscle, the musculature of the ureter possesses the inherent capacity to undergo rhythmic contractions. Rhythmic peristalsis plays an important part in propelling the renal secretion toward the bladder. Such contractions of the ureter persist, in the intact animal, following section of all its extrinsic nerves. Furthermore, they can be elicited, under proper conditions, in excised pieces of the ureter. Yet, ureteral activity probably is normally subject to regulatory nervous impulses. If, in an experimental animal, the kidney is actively secreting, peristaltic waves of contraction may be observed which are propagated along the ureter from the kidney to the urinary bladder in regular sequence. Direct stimulation of the ureter at any point gives rise to a contraction wave which is propagated in both direc-

tions from the point stimulated, thus peristalsis and antiperistalsis may be observed at the same time (Schilf, 1926).

Engelmann (1869) early came to the conclusion that the musculature of the ureter is stimulated automatically to undergo periodic contractions and its functional regulation requires neither intrinsic ganglion cells nor extrinsic nerves. Hryntschak (1925), in general, corroborated Engelmann's findings. Yet, the abundant nerve supply to the ureter cannot be regarded as devoid of functional significance.

Sympathetic stimulation apparently exerts little influence on the musculature of the ureter. Elliott (1906, 1907) observed no reaction of the ureteral musculature to stimulation of the hypogastric nerve nor to the administration of adrenalin. Lucas (1908) observed an increase in some cases; in others, a decrease in the tonus and force of contraction of the ureteral musculature following the administration of adrenalin.

The lower end of the ureter is not provided with a special sphincter muscle. The opening and closing of the ureter seems to be regulated by the activity of the bladder musculature and the internal vesical pressure. It is generally assumed that contraction of the bladder tends to close the ureter so that urine cannot be forced back into the ureters while the bladder is expelling its contents. Possibly, contraction of the bladder also results in reflex contraction of the lower portion of the ureter. This would also tend to prevent the back flow of urine into the pelvis of the kidney. Maintenance of the tonus of the ureteral musculature and reflex coordination of the activities of the ureter to contractions of the bladder probably represent the most important functions of the nerves supplying the ureter.

THE URINARY BLADDER.

Extrinsic Nerves.—The urinary bladder derives its extrinsic nerve supply directly from the vesical plexus which is a highly complex meshwork of nerve-fiber bundles and flattened ganglia extending from the region of the trigone along the lateral aspects of the bladder. This plexus receives fibers directly from the second, third, and fourth sacral nerves through their visceral rami, and from the upper lumbar nerves through the hypogastric plexus. It also receives fibers from the sacral portion of the sympathetic trunk through both the hypogastric and pelvic nerves (Müller, 1918). The pudendal nerve which supplies the external sphincter also includes afferent fibers to the internal sphincter and adjacent parts of the bladder. The pelvic and hypogastric nerves also convey afferent fibers to the bladder.

In general, it may be assumed that the preganglionic fibers involved in the parasympathetic supply to the bladder effect synap-

tic connections in ganglia situated outside the bladder wall. The correctness of this assumption cannot be demonstrated by anatomical data available at present. Certain physiological data also indicate that some of the preganglionic fibers in the parasympathetic supply effect synaptic connections in the ganglia incorporated in the vesical plexus. Both Müller (1918) and Dennig (1924) assumed that such is the case. While the majority of the preganglionic fibers involved in the sympathetic supply to the bladder probably

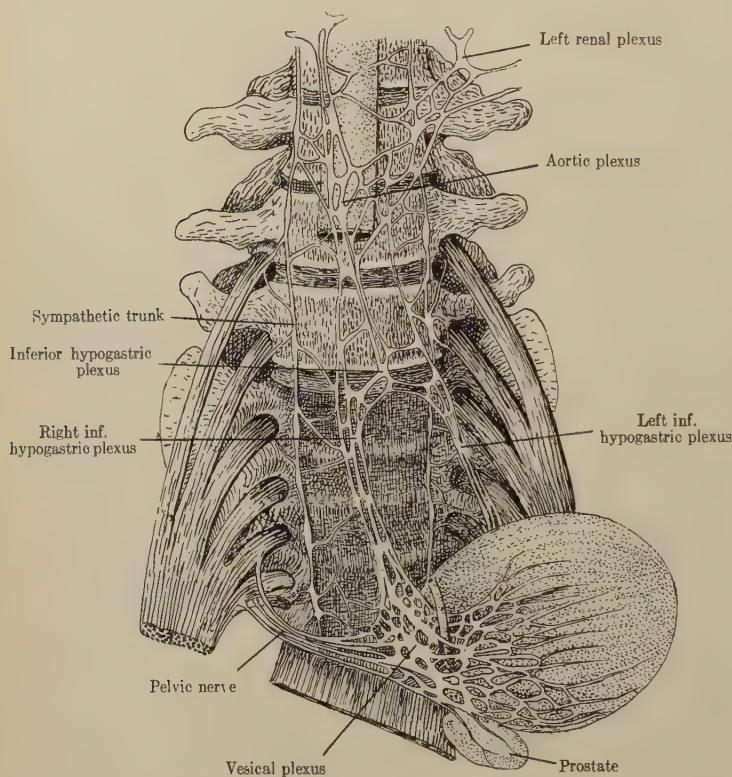


FIG. 50.—Diagrammatic illustration of the extrinsic innervation of the urinary bladder. (Modified from Greving.)

effect synaptic connections in the hypogastric and vesical plexuses, probably a small percentage terminate in the ganglia of the lumbar sympathetic trunk. In the dog, according to Schabadasch (1928), a large percentage of the extrinsic fibers enter the bladder wall without interruption in extrinsic ganglia.

Intrinsic Nerves.—The nervous mechanism in the wall of the bladder consists of numerous small ganglia and an abundant supply of nerve-fiber bundles arranged in a plexiform meshwork.

In general, the ganglia are situated at the nodal points in the plexus. The majority of the nerve-fiber bundles and ganglia occur in the musculature, but both nerve fibers and ganglia occur in the outer connective tissue layer and in the submucosa. In the bladder wall, the nervous elements are most abundant in the region of the trigone, and become increasingly less abundant as the distance from this area increases (Müller, 1918).

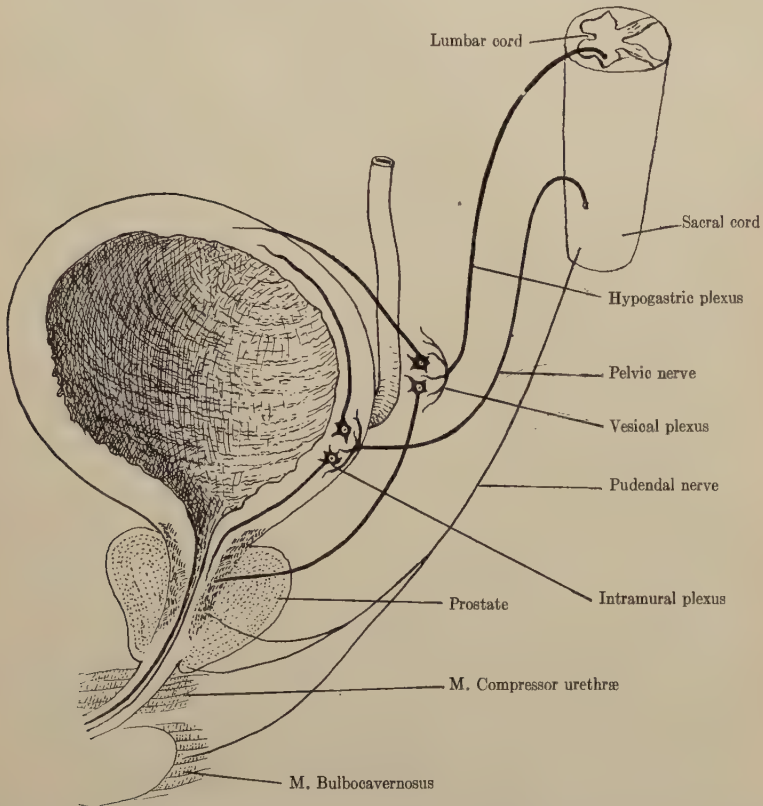


FIG. 51.—Schematic illustration of the bladder innervation. (Modified from Greving.)

The great majority of the nerve fibers in the bladder wall are unmyelinated fibers of small caliber. Myelinated fibers mainly of small caliber also occur in relatively small numbers. In general, the ganglia are not large, but relatively numerous. Not infrequently ganglion cells are also closely associated with intramural blood vessels. According to Müller (1918), the ganglion cells in the bladder are all multipolar. They are essentially similar to the neurons in the other abdominal plexuses.

In methylene-blue preparations of the frog's bladder, Müller (1918) described pericellular networks of very fine varicose fibers on the cell bodies, especially of those neurons which reacted lightly to the stain. These terminal networks were connected with varicose unmyelinated fibers which probably represent the terminal branches of preganglionic components of the sacral nerves. Such pericellular networks were not observed in preparations of the mammalian bladder. The terminations of nerve fibers in the musculature of the bladder conform to the usual type of motor nerve terminations in smooth muscle.

NERVE SUPPLY TO THE URETHRA.

The nerve supply to the urethra in the male is derived from the prostatic and cavernous plexuses. Both these plexuses include sympathetic fibers derived from the hypogastric plexus and parasympathetic components of the sacral outflow. As indicated by the results of experiments involving the use of nicotin, the sympathetic fibers supplying the urethra arise in the inferior mesenteric ganglion.

The prostatic plexus is continuous with the vesical plexus and is situated on both sides of the prostate gland. It supplies fibers to the prostate and the prostatic urethra and sends offsets to the neck of the bladder. The cavernous plexus of the penis represents a forward continuation of the prostatic plexus. Fibers arising from this plexus supply the membranous and penile portions of the urethra.

The uterine and vaginal plexuses in the female correspond to the prostatic plexus in the male. The vaginal plexus is composed mainly of parasympathetic components of the sacral outflow. The nerve fibers supplying the urethra and vagina are derived directly from the vaginal plexus. The external sphincter and the compressor urethræ muscles are supplied by the pudendal nerves.

NERVOUS CONTROL OF THE URINARY BLADDER.

Specific Effect of Sympathetic and Parasympathetic Nerves.—The urinary bladder is essentially a muscular organ whose function is the periodic discharge of the renal secretion. Its musculature consists of three layers of smooth muscle which are so intimately interwoven that the entire musculature constitutes a functional unit, the detrusor muscle. The outlet of the bladder is provided with an internal sphincter composed of smooth muscle and an external sphincter composed of striated muscle. As stated above, the bladder, including the internal sphincter, is innervated through the hypogastric (sympathetic) and pelvic (parasympathetic) nerves, and the external sphincter by the pudendal nerve.

Stimulation of the pelvic nerves elicits relaxation of the sphincter mechanism and contraction of the detrusor muscle resulting in expulsion of the contents of the bladder. Stimulation of the hypogastric nerves elicits increased tonus of the internal sphincter and relaxation of the detrusor muscle. In general, the sympathetic and parasympathetic innervation of the bladder may, therefore, be regarded as mutually antagonistic, although both components comprise both motor and inhibitory fibers, *i. e.*, the fibers of each component which are distributed to the sphincter muscles exert a functional influence which is the opposite of that exerted by the fibers of the same component which are distributed to the detrusor muscle. Taken as a whole, the result of parasympathetic stimulation is functional activity of the organ, while the result of sympathetic stimulation is inhibition of function.

Unilateral stimulation of the pelvic nerve elicits contraction of the corresponding lateral half of the detrusor muscle without materially affecting the other half. If one pelvic nerve has been cut several weeks previously, stimulation of the intact nerve results in contraction of the entire bladder musculature (Elliott, 1906, 1907). Bilateral section of the pelvic nerves results in marked atony of the detrusor muscle and closure of the sphincter (Dennig, 1924). After a few days, the bladder musculature, however, regains a certain degree of tonus and the emptying reflex is initiated earlier, in response to filling of the bladder, than is the case while the parasympathetic nerves are intact. Apparently, the bladder musculature is more irritable under these conditions than under normal innervation. Unless cystitis sets in, which is frequently the case following section of the pelvic nerves (Dennig, 1924), the animal may live on in spite of the disturbance of the bladder function.

The relaxation of the bladder which is brought about by stimulation of the hypogastric nerves is commonly preceded by an initial increase in tonus and is accompanied by increased tonus of the internal sphincter. The distribution of each hypogastric nerve is not limited to one lateral half of the bladder. Unilateral hypogastric stimulation elicits inhibition of the entire detrusor muscle, although such inhibition is usually not very marked. Bilateral section of the hypogastric nerve causes but slight disturbance of the bladder function. The only noticeable effect in most cases is more frequent micturition. According to Elliott, the hypogastric nerves exert no inhibitory influence on the bladder musculature in man. Certain investigators have also failed to observe any such influence in certain other mammals, particularly the dog, rabbit, and goat. Others have observed it in the dog.

Micturition.—Micturition is in part a reflex and in part a voluntary act. The nervous mechanism through which the voluntary control of this function is exercised has engaged the attention of not

a few investigators. An understanding of this mechanism is of fundamental importance not only for the understanding of the bladder function but also for the general understanding of cortical influences in the functioning of smooth muscle. This problem was recently subjected to an intensive experimental study by Dennig (1924), who concluded, on the basis of his findings, that cortical impulses are conducted by nerves which have been regarded as purely visceral. This conclusion is at variance with the accepted teaching that autonomic nerves do not convey cortical impulses. According to Müller (1918), the cortical impulses involved in voluntary micturition are not conveyed to the bladder musculature directly, but to the external sphincter which is a voluntary muscle. The peripheral fibers through which these impulses are conveyed are components of the pudendal nerve. Their direct effect is relaxation of the external sphincter. This, according to Müller's theory, gives rise to stimuli which are conveyed back to the spinal cord via the afferent pudendal fibers which effect reflex connections with efferent components of the pelvic nerves, *i. e.*, the micturition reflex is initiated by voluntary inhibition of a striated muscle, and is carried out as a spinal reflex through the appropriate visceral efferent chains, like the spinal reflexes involved in the functional control of other visceral organs. Dresel (1923) advanced the opinion that the micturition reflex may be elicited by voluntary contraction of the abdominal muscles. According to Adler (1918), the internal sphincter is caused to relax voluntarily, which in turn brings about reflex relaxation of the external sphincter and contraction of the detrusor muscle.

The theory advanced by Müller has recently been supported by experimental data obtained by Barrington (1921). He was able to show, following section of the urethra just below the bladder in decerebrated cats, that contraction of the detrusor muscle could be elicited by the passage of liquid through the distal portion of the urethra. Obviously, the reflex in question was carried out over afferent fibers of the pudendal and efferent fibers of the pelvic nerve. The same reflex was also obtained by Dennig (1924) in the dog. In his experiments, the contraction of the detrusor muscle always took place at the instant in which the pressure in the urethra became sufficient to open the external sphincter, regardless of the direction of the flow of the liquid. The mere flowing of liquid through the distal part of the urethra did not, in his experiments, elicit contraction of the bladder. He concluded, therefore, that the adequate stimulus for the micturition reflex was afforded by the opening of the external sphincter. Müller's theory was thus verified by experimental demonstration.

Dennig has shown experimentally that voluntary micturition can still be carried out following section of the pudendal nerves.

Although the closure of the sphincter mechanism is less perfect following bilateral section of the pudendal nerve than before, dogs which had previously been trained to micturate at a designated place persisted in this habit after section of the pudendal nerves and discharged urine voluntarily whenever they were brought to the place in question. This seems to prove that voluntary micturition may still be carried out in the absence of intact pudendal nerves. Since no other somatic efferent fibers reach the bladder or urethra, and the direct stimulating effect on the bladder of increased intra-abdominal pressure due to contraction of the abdominal muscles was ruled out by reason of the ease with which the flow of urine was brought about, Dennig concluded that voluntary impulses affect the bladder directly through the autonomic nerves. Further experimentation also proved that the autonomic nerves involved are the parasympathetic and not the sympathetic nerves supplying the bladder. Following section of the pudendal nerves, section of the hypogastric nerves had no apparent effect on voluntary micturition. Voluntary micturition could not be carried out, however, following section of the pelvic nerves, leaving only the hypogastric nerves intact, until the bladder became adjusted so that it would contract in response to increased intra-abdominal pressure due to contraction of the abdominal muscles.

The experimental results obtained by Barrington (1921) also shed new light on the sequence of events involved in reflex micturition. According to his findings in decerebrate animals, distention of the bladder through filling elicits reflex contraction of the bladder musculature. This in turn elicits reflex relaxation of the urethra. Relaxation of the urethra elicits further contraction of the bladder musculature resulting in complete emptying of the bladder. These reflexes are carried out in part through the spinal cord and in part through higher central nervous centers.

In addition to showing that voluntary micturition may be carried out in the absence of functional pudendal nerves, *i. e.*, through the autonomic (parasympathetic) innervation of the bladder, Dennig's experimental results also throw new light on the specific functional defects of the bladder due to elimination of any one of the several components of its nerve supply. Section of the pudendal nerves results in imperfect closure of the sphincter and loss of urethral sensibility, but does not materially disturb the normal functioning of the bladder otherwise. Section of the hypogastric nerves either alone or in addition to the pudendal nerves results in no marked changes in bladder function. Section of the pelvic nerves, however, brings about profound functional and trophic disturbances of the bladder. Section of all the nerves to the bladder is followed by more or less constant flow of urine in small quantities, but also periodic discharges of larger quantities brought about by mechanical stimuli

to which the bladder is now hypersensitive. Incomplete emptying and cystitis are common under these conditions.

Bladder Sensibility.—Although the internal sphincter vesicæ is composed of smooth muscle, it probably receives its afferent innervation at least in part through the pudendal nerves. Adler (1920) advanced the opinion that contractions of the internal sphincter gives rise to afferent impulses which result in the urge to voluntary micturition. On the other hand, Schwartz (1920) advanced the theory that the impulses which result in the desire to micturate arise by reason of contraction of the detrusor muscle. Both conceptions probably are at least in part correct. Experimental evidence suggests that contractions of both the detrusor muscle and the internal sphincter play a part in the urge to voluntary micturition. The sensations involved are not all of the same quality. Indefinite sensations referred to the region of the bladder but not definitely localized probably result from impulses arising in the bladder musculature, while the more acute sensations which can be more or less definitely localized at the neck of the bladder are brought about by afferent impulses arising in that region (Müller, 1924). By reason of the physiological character of the parasympathetic fibers distributed to the internal sphincter muscle, contraction of the detrusor muscle also tends to bring about reflex relaxation of the internal sphincter. Under these conditions, emptying of the bladder can only be prevented by voluntary contraction of the external sphincter. If the external sphincter holds, a short period of rest usually ensues during which the detrusor muscle relaxes somewhat and relieves the intravesical pressure. If the bladder is not voluntarily emptied, stronger contractions of the detrusor muscle set in and, if they succeed in pressing a few drops of urine into the urethra, the impulse to micturate becomes irresistible and reflex micturition takes place. If the external sphincter mechanism withstands the pressure produced by repeated contractions of the detrusor muscle, this muscle may become inactive, so that soon after the urge to micturate was at its maximum strength spontaneous micturition becomes impossible.

According to Schwartz, voluntary micturition is preceded by a sudden increase in intravesical pressure. He regarded this as the cause of the emptying reflex; Müller, on the other hand, regarded it as the beginning of the emptying process. He pointed out that increased intravesical pressure alone does not give rise to a flow of urine, under physiological conditions, but that the primary cause of micturition is distention of the bladder wall.

The above observations show clearly that impulses arising in the bladder give rise to sensations which can be more or less definitely localized. They afford no adequate basis, however, for any con-

clusion regarding the afferent pathways through which these impulses reach the central nervous system.

According to Fröhlich and Meyer (1922), electrical stimulation of the fundus of the bladder gives rise to afferent impulses mediated through the pelvic nerves which result in painful sensations. Similar stimulation in the region of the sphincter gives rise to afferent impulses mediated through the pudendal nerve which also result in painful sensations. These results afford definite information regarding the afferent pathways of impulses arising in circumscribed areas of the bladder, but do not afford any unmistakable clues regarding the pathways of afferent impulses which result in the desire to micturate.

In Dennig's experiments, marked distention of the bladder by filling it through a catheter resulted in uneasiness on the part of the animal. If the distention elicited reflex contraction of the bladder musculature, the animal exhibited increased uneasiness until the liquid began to escape along the catheter and the internal pressure was reduced. Section of the pudendal nerves had no apparent effect on the uneasiness manifested by the animal due to artificial distention of the bladder. When both hypogastric and pelvic nerves were cut, leaving the pudendal nerves intact, the uneasiness manifested by the animal was much less marked. Following section of all the nerves to the bladder, the animal no longer manifested any uneasiness, regardless of the extent to which the bladder was artificially distended. It may be assumed, therefore, that the pelvic or hypogastric nerves play the major rôle in the conduction of afferent impulses which result in the urge to voluntary micturition. This function probably is subserved mainly by the pelvic nerves. Clinical observations indicate, however, that the hypogastric nerves also play a part in such afferent conduction (Riddoch, 1917). Neither should the conduction of afferent impulses by the pudendal nerves be regarded as unimportant in the urge to voluntary micturition. The impulses which give rise to sensation of emptying of the bladder are probably mediated through the pudendal nerve (Dennig).

Central Nervous Centers Involved in Bladder Function.—The visceral efferent neurons whose axons reach the urinary bladder via. the pelvic nerves are located in the same segments of the sacral spinal cord from which the pelvic nerves arise. Many of the reflexes involved in the nervous control of the bladder functions are carried out through reflex centers in this portion of the cord, the afferent limbs of the reflex arcs in question being components of the pelvic and pudendal nerves.

Bladder reflexes elicited by afferent stimulation of other nerves may also be mediated through the sacral centers. Following tran-

section of the spinal cord in the lumbar or thoracic region in the dog, afferent stimulation of the sciatic nerve still elicits reflex emptying of the urinary bladder. Following interruption of the spinal cord in the lumbar or higher levels in man, abduction of the legs or cutaneous stimulation of the external genitalia may be sufficient stimulus to elicit reflex emptying of the bladder. Following destruction of the sacral spinal cord in animals or pathological lesions in this part of the cord in man, cutaneous stimulation no longer elicits bladder reflexes (Müller, 1924).

The preganglionic neurons involved in the sympathetic supply to the bladder are located in the upper lumbar segments of the spinal cord. Impulses going out from these cells exert an inhibitory influence on the detrusor muscle and augment the tonus of the internal sphincter. These effects on the bladder may also be elicited reflexly through centers in the lumbar spinal cord. While sympathetic reflexes are far less important in the normal functional control of the urinary bladder than parasympathetic reflexes, it must be admitted that centers in the lumbar spinal cord play a part in the reflex control of bladder functions.

The sacral and lumbar spinal centers which are involved in the reflex control of the bladder mediate not only bladder reflexes elicited by afferent impulses coming from the lower parts of the body, but also bladder reflexes elicited by afferent impulses arising within or at the surface of higher parts of the body. The bladder, like the blood vessels, is highly sensitive to painful stimulation in any part of the body and responds by contraction of its musculature. It cannot be assumed that all peripheral sensory fibers effect direct reflex connections with the spinal centers from which efferent impulses may reach the bladder; therefore, it must be assumed that pain, and perhaps also epicritic and temperature sensations, modify the general irritability of the gray substance of the spinal cord and that these tonus changes which probably arise in the gray matter of the posterior horns affect the spinal bladder centers and thus bring about changes in the tonus of the bladder musculature (Müller, 1924).

The bladder musculature is also influenced by impulses emanating from the diencephalic autonomic center. Psychic influences on the bladder probably are mediated through this center. Strong emotional disturbances, *e. g.*, anxiety or fright, not uncommonly give rise to an urge to micturate and may, under certain conditions, actually result in involuntary micturition. The suggestion offered by the sound of running water or even the thought of voiding the bladder may also give rise to an almost irresistible urge to micturate. It cannot be assumed that such psychic stimulation of the detrusor muscle arises in the cerebral center which is the seat of voluntary impulses. Not infrequently psychic influences give rise to an urge

to micturate in the presence of voluntary effort to suppress it. It seems more probable, therefore, that bladder reactions to psychic influences are mediated through the autonomic center in the diencephalon or other centers in the brain stem.

Nevertheless, it must be admitted that the bladder also reacts to direct cortical influences. Furthermore, certain experimental and clinical data support the theory that the bladder is represented in a definite area in the voluntary cortex. Kleist observed that micturition is always interfered with in cases of bilateral paralysis of the lower extremities. He concluded, therefore, that impulses to the bladder arise in the precentral gyrus; perhaps also in the paracentral lobule. He also pointed out that only a bilateral pyramidal lesion could disturb the bladder function, since the effect of a unilateral lesion would be compensated by the intact pyramidal neurons on the opposite side. He pointed out further that cortical bladder disturbances sometimes manifest themselves in incontinence and sometimes in retention of urine, but are usually of relatively short duration. Brüning also observed retention of urine due to pyramidal disturbances in two operative cases. On the basis of the findings in these cases, he concluded that cortical impulses to the bladder arise in the portion of the precentral gyrus which supplies the lower extremities. Pfeiffer also concluded, on the basis of clinical observations, that the bladder is represented in the portion of the precentral gyrus which supplies the hip. On the other hand, Forster localized the voluntary bladder center in the paracentral lobule, *i. e.*, on the median surface of the cerebral hemisphere. Adler (1919) attempted to reconcile these apparently conflicting views by assuming the existence of cells which supply the external sphincter in the portion of the precentral gyrus which supplies the hip and of cells which give rise to impulses which are conveyed to the internal sphincter in the motor area which supplies the foot. In a later paper, Adler (1920) postulated another center in the gyrus fornicatus in which bladder sensations arise, and still a fourth in the frontal lobe, to which the other three are subordinated.

While admitting a direct cortical influence on bladder function, Müller (1924) properly called attention to the fact that no other visceral organ is known to be represented in a localizable area in the cerebral cortex. He assumed that the same principles govern the bladder functions in so far as they are subject to voluntary control, and advanced the opinion that the voluntary control of the bladder functions can be accounted for without assuming direct representation of the bladder in a localizable area of the cerebral cortex. This opinion is in complete accord with current conceptions regarding the voluntary control of other visceral functions. If Dennig's observation, that a degree of voluntary control of the bladder functions still persists following bilateral section of the pudendal

nerve should be confirmed, however, the conclusion that some direct cortical influence is exerted on the bladder through its visceral innervation would be unavoidable. Further experimental investigation of this problem is highly desirable.

Nervous Control of the Urethra.—The smooth muscle in the wall of the urethra, like the internal sphincter vesicæ, relaxes during active contraction of the detrusor muscle. Likewise, it undergoes tonic contraction simultaneously with the internal sphincter. Contraction of the smooth musculature of the urethra, like that of the internal sphincter, is brought about by stimulation of its sympathetic innervation, while relaxation of this musculature is brought about by stimulation of its parasympathetic innervation. The effect of the sympathetic and parasympathetic nerves respectively on the urethra is the opposite of their effect on the detrusor muscle. This may be regarded as a functional adaptation to facilitate the flow of urine during micturition and to support the sphincter mechanism during relaxation of the detrusor muscle and filling of the bladder. As in the case of the internal sphincter, the voluntary contraction and relaxation of the external sphincter and the compressor urethræ muscles also plays a rôle in the reflex nervous regulation of the smooth musculature of the urethra.

CHAPTER XIII.

INNERVATION OF THE SEX ORGANS.

THE MALE SEX ORGANS.

Macroscopic Anatomy.—The testis receives its innervation through the spermatic plexus which also constitutes the major portion of the nerve supply of the spermatic cord. The spermatic plexus is derived mainly from the aortic plexus, but also receives fibers from the renal plexus. It invests the spermatic artery throughout its course and communicates with the hypogastric plexus on the lower part of the ductus deferens. The preganglionic and visceral afferent fibers involved in the sympathetic innervation of the testis in man are components of the tenth thoracic nerve. The afferent fibers supplying the epididymis reach the spinal cord through the eleventh and twelfth thoracic and first lumbar nerves. In the cat and rabbit, according to Langley and Anderson (1895), the preganglionic and visceral afferent fibers involved in the sympathetic innervation of the sex organs are components of the second to the sixth lumbar nerves.

The nerve supply to the seminal vesicle and ductus deferens is derived from the hypogastric plexus. This plexus gives rise to a subordinate plexus which supplies the seminal vesicle and continues along the ductus deferens as far as the epididymis. The epididymis receives fibers from both the hypogastric and the spermatic plexus.

The prostatic plexus is a relatively large plexus lying on either side of the prostate gland. It includes both sympathetic and parasympathetic components. The former are derived from the hypogastric plexus; the latter from the sacral parasympathetic outflow. In addition to supplying the substance of the prostate and the prostatic urethra, the prostatic plexus gives rise to the cavernous plexus of the penis. The latter plexus gives rise to nerves which supply the corpora cavernosa penis and, communicating with branches of the pudendal nerves, sends rami to the corpus cavernosum urethræ and the penile portion of the urethra. The retractor muscle of the penis, which occurs in many mammals, derives its nerve supply from the same sources as the smooth muscle of the urethra (Langley and Anderson, 1895).

The glans and skin of the penis are supplied exclusively by branches of the dorsal nerve of the penis. This nerve arises from the pudendal nerve, and consists of fibers derived from the third

and fourth sacral nerves. The compressor urethræ and ischiocavernosus and bulbocavernosus muscles, viz.: the voluntary muscles employed in the act of ejaculation, are also innervated by branches of the pudendal nerve. Furthermore, vasoconstrictor fibers derived

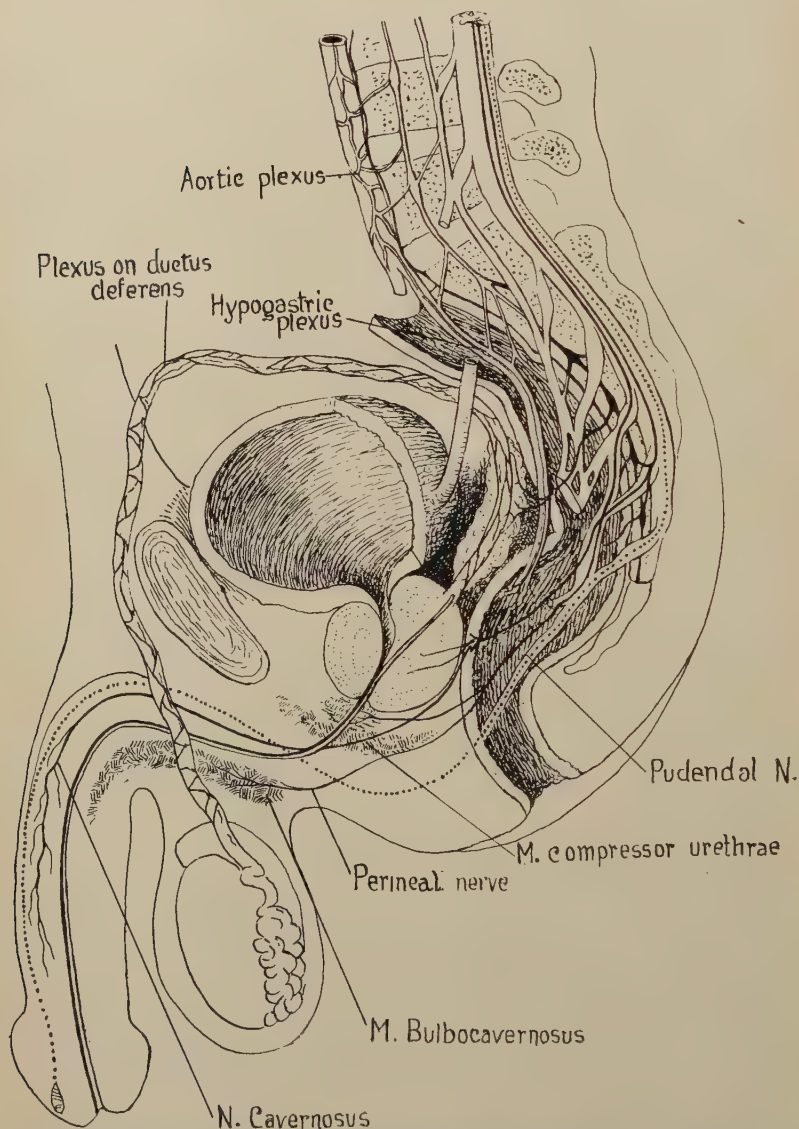


FIG. 52.—Schematic illustration of the innervation of the male sex organs. Dotted line indicates afferent cerebrospinal fibers; double lines indicate sympathetic nerves; heavy black lines indicate parasympathetic nerves.

from the hypogastric plexus join the pudendal nerve to be distributed through its branches to the blood vessels of the penis.

Microscopic Anatomy.—The spermatic plexus is a relatively rich meshwork made up largely of unmyelinated nerve fibers, but also including myelinated fibers. In the spermatic cord, it gives rise to numerous slender fiber bundles which, in general, are more or less closely associated with the blood vessels. Slender filaments derived from the spermatic plexus become associated with the ductus deferens and join the plexus on this duct. Farther distally, nerve fibers become associated with the ductus epididymis and supply the thin layer of smooth muscle in the wall of this duct. Slender rami also occur among the ductuli efferentes. The majority of these are closely associated with blood vessels, but also supply fibers to the very thin layer of smooth muscle in the walls of these ducts (Kuntz, 1919).

The distribution of nerve fibers in the testis has been described by many investigators. Letzerich (1868) claimed to have traced fibers from nerves lying in the connective tissue between the seminiferous tubules through the membrana propria to their terminations on cells in the deeper layers of the seminal epithelium. Retzius (1893) was unable to substantiate this finding. In Golgi preparations of the testis of the cat, he observed nerve fibers which seemed to penetrate the membrana propria in small numbers, but was unable to demonstrate the terminations of these fibers in the seminal epithelium. Timofeew (1894), who studied the distribution of nerve fibers in the spermatic cord and testis in various mammals (rabbit, guinea-pig, rat, cat, dog), described a rich plexus associated with the blood vessels, ductus deferens, and ductus epididymis. He also observed nerve fibers in proximity to the seminiferous tubules, but was unable to find any fibers which penetrate the membrana propria. He regarded the nerve fibers which appear on the surface of the seminiferous tubules as fibers which supply small blood vessels. Cavalie (1902) described a rich plexus of nerve fibers associated with the blood vessels and seminiferous tubules in preparations of the testis of the fowl and rabbit. He also described terminal arborizations of these fibers among the cells in the deepest layers of the seminal epithelium and, in the rabbit, about the epithelial cells in the ductus epididymis. Loisel (1902) also described nerve fiber terminations on both spermatogenic and sustentacular cells in the deep layers of the seminal epithelium.

In a study of the innervation of the testis of the dog by the use of the pyridine-silver method, the writer (1919) found nerve-fiber bundles in abundance in proximity to the vessels in the mediastinum testis and in the connective tissue between the seminiferous tubules, but none were found to penetrate the membrana propria of the seminiferous tubules. An exhaustive search also failed to reveal

any nerve fibers which terminate in relation to the interstitial secretory cells. The general distribution of nerve fibers in the testis seems to be determined by the distribution of the arteries and veins. Areas of connective tissue between the seminiferous tubules which contain no blood vessels except capillaries contain very few nerve fibers. Doubtless, these are associated with the capillaries. Neither do nerve fibers invade areas of interstitial secretory tissue except as they accompany blood vessels. If the seminal epithelium or the interstitial secretory tissue were innervated, we should expect to find a more uniform distribution of nerve fibers in the connective tissue between the seminiferous tubules.

Numerous nervous rami of relatively large size occur in the tunicae albuginea and vasculosa. These rami run a somewhat tortuous course and do not always appear to be closely related to blood vessels, but fiber terminations other than those in the walls of the blood vessels were not observed in our preparations. That sensory nerve terminations may occur in these layers seems highly probable.

These findings are in general accord with those of earlier investigators cited above, except with respect to the occurrence of nerve fiber terminations in the seminal epithelium. Pines and Maiman (1927) also failed to find nerve fiber terminations in the seminal epithelium. They described end-knobs in contact with the walls of the seminiferous tubules, but obtained no evidence that nerve fibers penetrate the membrana propria. Contrary to our findings, they described terminations of unmyelinated fibers among the interstitial secretory cells, which they regarded as the terminations of secretory fibers. They also described coarser fibers terminating in end-bulbs in the connective tissue, but not in relation to the blood vessels. They regarded these fibers as sensory in function.

In view of the above findings and the physiological data available at present, the existence of a direct nerve supply to the seminal epithelium must be regarded as extremely doubtful. Neither do we regard the evidence for the existence of secretory fibers to the interstitial secretory tissue, advanced by Pines and Maiman, as conclusive in the absence of other corroborative data.

The prostatic plexus, the plexus of the seminal vesicle, and the cavernous plexus of the penis were described in detail by Müller and Dahl (1912). These plexuses are made up of both sympathetic and parasympathetic components and exhibit a similar microscopic structure. They are composed mainly of unmyelinated, but also contain numerous myelinated fibers. In the fatty connective tissue between the prostate gland and the seminal vesicle occur numerous very small, flattened ganglia, some of which are incorporated in the prostatic plexus, and others in the plexus on the seminal vesicle. Nerve fibers may also be traced from these plexuses into the pros-

tate gland and seminal vesicle. Small ganglia also occur in the cavernous plexus of the penis. None were found in the plexus on the ductus deferens. The neurons in the small ganglia in these plexuses are relatively small and exhibit numerous short dendrites, which in general terminate within the cell capsule. In this respect they differ from the majority of the neurons in the ganglia of the sympathetic trunk. Müller and Dahl were inclined to regard them as neurons of a distinct type, although the ganglia of the sympathetic trunk also contain neurons in small numbers whose dendrites do not penetrate the cell capsule. Inasmuch as some of the dendrites of neurons in these small ganglia also penetrate the cell capsule, there seems to be no adequate reason to regard the neurons in these plexuses as a distinct morphological type. They probably fall within the range of normal morphological variation of autonomic neurons in general. No ganglion cells were found within the prostate gland or the seminal vesicle. Both these structures are penetrated by both unmyelinated and myelinated nerve fibers, but the terminations of these fibers have not been described.

The nerves which arise from the cavernous plexus of the penis contain relatively few myelinated fibers. In addition to supplying the membranous and penile portion of the urethra they also supply the blood vessels and smooth muscle of the corpora cavernosa penis, corpus cavernosum urethræ, and the skin of the penis.

Sense organs in the glans penis have been described by numerous investigators. They occur in considerable abundance in both the superficial and deeper layers of the chorium. They have been variously regarded as similar to Pacinian corpuscles, end-bulbs of Krause, and sense organs which are characteristic for the external genital organs. While they exhibit a wide range of variation in various mammals, they probably do not differ essentially from the cutaneous sense organs found in other parts of the body. They are connected with the terminal branches of afferent fibers which are incorporated in the dorsal nerve of the penis and reach the spinal cord through the pudendal nerve. According to Sklavunos (1894), nerve fibers also terminate directly in the epithelium of the glans.

Nervous Control of the Male Sex Organs.—Effects of Sympathetic and Parasympathetic Stimulation.—Our knowledge of the rôle of nervous influences in the regulatory control of the functions of the male sex organs is based mainly on the findings of the older physiologists. Recent investigations have added much to our knowledge of the general physiology of the male reproductive system, but little that bears directly on the rôle of nervous regulation in the functioning of this system.

Budge (1858) observed that electrical stimulation of the communicating rami of the third and fourth lumbar nerves in the rabbit elicits contractions of the ductus deferens which are propagated

from the testis toward the seminal vesicles. Stimulation of the inferior mesenteric ganglion or the hypogastric nerves elicits the same reaction of the ductus deferens, but stimulation of the aortic plexus above the inferior mesenteric ganglion calls forth no reaction of the ductus deferens. These findings established the important fact that the spinal center through which motor activities of the ductus deferens and seminal vesicle are mediated is located in the lumbar segments of the spinal cord.

Eckhardt (1863) found that electrical stimulation of the visceral rami of the sacral nerves in the dog elicited erection of the penis. He, therefore, designated these rami the "*nervi erigentes*." He also observed that stimulation of these nerves results in expulsion of the prostatic secretion. On the other hand, he was unable to elicit any reaction of the penis by electrical stimulation of the pudendal nerve. He observed, however, that mechanical stimulation of the glans no longer resulted in erection of the penis following section of the pudendal nerve. Neither could he bring about erection by painful stimulation of the central end of the severed pudendal nerve. These findings established the important rôle of the pelvic nerves in the process of erection and also suggested the rôle of the afferent pudendal fibers in erection elicited by stimulation of the glans.

Nikolsky (1879) observed that section of the *nervus erigens* is followed by contraction of the blood vessels in the penis and that electrical stimulation of the peripheral end of this nerve elicit dilatation of the blood vessels and filling of the sinuses in the erectile tissue. Frank (1895) also observed vasodilatation of the penis in response to stimulation of the *nervus erigens*. He also determined experimentally that the fibers which join the pudendal nerve from the hypogastric plexus exert a constrictor effect on the blood vessels of the penis.

Mislawsky and Bormann (1898) observed that in addition to their motor effect on the musculature of the ducti deferentia and seminal vesicles, the hypogastric nerves also exert a true secretory influence on the prostate gland. Certain experimental data recently reported by Mislawsky (1927) indicate that the prostate receives both secretory and inhibitory fibers.

According to Langley and Anderson (1895), stimulation of the lumbar communicating rami or the lower lumbar sympathetic trunk in animals (rabbit, cat, dog) results in constriction of the blood vessels in the penis as well as contraction of the retractor penis muscle. On the basis of their experimental results, they concluded that the preganglionic fibers involved in vasoconstriction in the external genitalia are components of the second, third, fourth, and sometimes also the first lumbar nerves. They found no satisfactory evidence that the lumbar nerves contain vasodilator or inhibitory

fibers for the external genitalia. Following section of the lumbar nerves or extirpation of the lower lumbar portion of the sympathetic trunks, mild erection may come about by reason of the removal of the vasoconstrictor influence of the hypogastric nerves. Langley and Anderson, like various other investigators, also confirmed the finding of Budge, that stimulation of the lumbar nerves elicits contraction of the entire musculature of the ducti deferentia and seminal vesicles. Furthermore, the results of their experiments involving the sacral nerves led them to conclude that "the sacral nerves send neither motor nor inhibitory fibers to any of the internal generative organs."

Spina (1897) observed erection and ejaculation in the absence of stimulation of the genitalia in a guinea-pig following transection of the spinal cord in the lower thoracic region. He also observed that if the spinal cord is destroyed, in a guinea-pig, by passing a slender rod downward through the vertebral canal, ejaculation without erection is elicited when the end of the rod reaches the lumbar region.

Müller (1901) reported the results of experiments in which dogs which had been subjected to extirpation of the lower lumbar and sacral portions of the spinal cord, in spite of the paralysis of the posterior portions of the body, exhibited erection in the presence of a rutty female. On the other hand, dogs which had been subjected to extirpation of the lower thoracic and upper lumbar portions of the spinal cord, leaving the lower lumbar and sacral portions intact, exhibited sexual excitement, but no erection in the presence of a rutty female. Pressure on the abdomen which resulted in emptying of the bladder, in these dogs, also resulted in reflex erection of the penis. Likewise, reflex erection could be elicited by direct stimulation of the glans or shaft of the penis, but none of these stimuli elicited ejaculation in these dogs.

Reflex Centers in the Spinal Cord.—The results of animal experimentation cited above clearly indicate the existence of a center in the sacral spinal cord which mediates reflex erection, and another in the lumbar spinal cord which mediates reflex ejaculation. There is no conclusive evidence that either the erection or ejaculation reflex can be carried out through the plexuses associated with the genital organs alone, either in the intact animal or following destruction of the centers in question. The results of Müller's experiments cited above indicate that erection may be brought about by psychic stimulation following destruction of the sacral spinal cord, but not following destruction of the lumbar cord. This experimental finding is also corroborated by clinical observations (Müller, 1901). It must be assumed, therefore, that in the absence of the sacral center the efferent impulses involved in bringing about erection due to psychic stimulation are mediated through the lumbar center. Apparently, the lumbar center may, under these conditions, to a

certain extent, subserve the functions of the sacral center. This seems to indicate the existence of fibers in the lumbar nerves which may, at least under certain conditions, bring about vasodilatation in the penis, although Langley and Anderson found no experimental evidence for the existence of such fibers.

In view of all the data available, the existence of a sacral center which mediates erection and a lumbar center which mediates ejaculation may be regarded as established. Possibly, the lumbar center may, under certain conditions, mediate erection, but ejaculation cannot be mediated through the sacral center. Reflex erection and ejaculation can only be carried out through these centers.

Erection.—Although the act of erection may be carried out as a pure reflex reaction, it commonly involves psychic stimulation, and is subject in a large measure to voluntary influences, but cannot be carried out as a direct voluntary act. Impulses received through any of the special senses, including touch, may call forth the psychic manifestations of sexual excitation. In the absence of specific afferent stimulation, sexual excitation may arise as the result of suggestion, sensual associations, or desires in which previous experience plays an important rôle. Furthermore, sexual excitation may be brought about by afferent impulses arising within the visceral organs, particularly the sexual apparatus. Such impulses are probably determined in a large measure by internal secretory activity, not only of the sex glands, but also of other endocrin organs. The functional balance of the several endocrin organs probably plays an important rôle in determining the threshold of irritability, not only of the erectile center, but also of the nervous mechanisms involved in the psychic manifestations of sexual excitation.

Under normal conditions, reflex erection commonly subsides as soon as the stimulation which called it forth ceases. Long-continued engorgement of the erectile tissue must be regarded as pathological. Neither does erection called forth by psychic stimulation continue but for a limited period. If ejaculation occurs, the same stimulation which elicited contraction of the ducti deferentia and seminal vesicles also elicits vasoconstriction in the erectile tissue, thus the turgor of this tissue is relieved. The same stimulation also elicits reflex contraction of all the smooth muscle in the penis; consequently, this organ may temporarily be reduced to less than its normal size. In animals in which the penis is provided with a retractor muscle, the reflex reaction associated with ejaculation includes contraction of the retractor muscle, resulting in retraction of the organ. The impulses involved in this entire reaction are mediated through the lumbar center and the hypogastric nerves.

Contraction of the smooth muscle in the corpora cavernosa and skin of the penis and vasoconstriction in the erectile tissue may also be called forth by psychic influences which counteract sexual desire,

e. g., disgust or fear. Likewise, reflex contraction of this musculature may be elicited by cold applications to the skin of the organ or neighboring areas, including the upper portions of the thighs. Temporary contraction of the penis, therefore, occurs not uncommonly during a cold bath. On the other hand, vasodilatation and engorgement of the erectile tissue may be elicited reflexly by warm applications to the parts in question or by a warm bath.

Ejaculation.—Ejaculation is not a necessary accompaniment of erection. In normal healthy individuals in the waking state, the discharge of seminal fluid is normally elicited only by stimulation of the glans. Furthermore, the reaction is to a large extent dependent on the quality of the stimulus. Simple contact, electrical or thermal stimulation, or painful stimuli do not usually elicit ejaculation. The adequate stimulus seems to be gentle friction, particularly of the moist glans. The necessary duration of such stimulation depends on conditions affecting the individual, *viz.*: his general physical condition, age, psychic excitability, and the secretory content of the sex glands.

Ejaculation is essentially a reflex reaction. The afferent impulses are received through the sense organs in the glans and conveyed to the spinal cord through afferent components of the pudendal nerves. The afferent impulses involved arise in the upper lumbar segments of the spinal cord and traverse the lumbar rami communicantes and hypogastric nerves. Ejaculation cannot be elicited following extirpation or destruction of the lumbar spinal cord (Müller, 1901).

Inasmuch as stimulation of the glans must, under normal conditions, be continued at least for a short interval in order to elicit ejaculation, this reaction must involve the summation of impulses. This summation probably occurs in the ejaculatory center in the lumbar spinal cord. When it has reached a certain level, a sudden discharge of efferent impulses takes place which calls forth sudden contraction of the smooth musculature of the entire internal sexual apparatus, resulting in the propulsion of seminal fluid into the proximal portion of the urethra. This results in reflex contraction of the striated constrictor urethræ, bulbocavernosus, and ischiocavernosus muscles which brings about the expulsion of the seminal fluid from the urethra. Consequently, the ejaculatory act is completed by the reflex contraction of voluntary muscles.

According to Müller and Dahl (1912), the spinal reflexes involved in the contraction of the constrictor urethræ and ischiocavernosus and bulbocavernosus muscles during ejaculation are mediated through the ejaculatory center in the lumbar spinal cord. If such is the case, this fact further supports the theory that the summation of impulses involved in the ejaculatory reaction takes place in the spinal cord.

The discharge of seminal fluid may take place during sleep

(nocturnal emission) in the absence of specific stimulation of the glans. The adequate stimulus involved in nocturnal emission is not known. It has been generally assumed that erotic dreams constitute an important factor in this reaction. Yet, similar psychic manifestations during the waking state, at least in healthy individuals, do not call forth the discharge of seminal fluid. It may be assumed, therefore, that certain inhibitory influences which prevent this reaction to psychic stimulation during the waking state are not effective during sleep. On the other hand, it may well be that erotic dreams are a consequence rather than the cause of nocturnal emissions. That the discharge of seminal fluid during sleep, as well as during the waking state, gives rise to afferent impulses which result in psychic manifestations is certain. Possibly, erotic dreams associated with nocturnal emissions are to be regarded only as the outcome of such psychic manifestations. It seems highly probable that the discharge of seminal fluid may be called forth reflexly during sleep by the stimulus afforded by internal pressure, particularly in the seminal vesicles and prostate gland by reason of the accumulation of seminal and prostatic secretion. The data available at present do not afford an adequate basis for the complete understanding of this sexual phenomenon.

The Sexual Orgasm.—The sensations immediately associated with ejaculation constitute the sexual orgasm. They arise simultaneously with the initiation of the peristaltic contraction of the ducti deferentia. Consequently, the beginning of the orgasm precedes the expulsion of the seminal fluid from the urethra by a short interval.

How and where the sensations which constitute the sexual orgasm arise is not definitely known. The afferent impulses involved probably arise in the genital organs as a result of the contraction of the smooth musculature involved in the ejaculation reflex. These impulses are conveyed to the spinal cord by the visceral afferent fibers distributed to this musculature and reach the cerebral cortex in the same manner as other visceral impulses which give rise to sensations. Inasmuch as sexual sensations are essentially of a primitive type, it need not be assumed that all the afferent impulses which play a part in sexual feeling or awareness reach the cerebral cortex. Many of them probably do not ascend beyond the thalamus.

The impulses which give rise to the sexual orgasm also call forth reactions in other visceral organs. The excitation apparently spreads throughout the entire autonomic nervous system. Both the rate and force of the cardiac contractions are augmented, respiration is stimulated and not uncommonly perspiration may be called forth. These impulses also give rise to somatic reflexes. In addition to the contractions of the compressor urethræ and ischio-cavernosus and bulbocavernosus muscles which play a part in the expulsion of the seminal fluid, spastic contractions of the extensor

muscles of the lower extremities not uncommonly occur simultaneously with the orgasm. According to Müller and Dahl (1912), the reflexes involved in these somatic reactions are carried out through reflex centers in the spinal cord. They observed clonic contraction of the extensor muscles of the hind limbs simultaneously with the expulsion of seminal fluid elicited by artificial stimulation of the glans of the erect penis in a dog following transection of the spinal cord above the lumbar region.

Cortical Influences.—As pointed out above, the anatomical data available do not justify the conclusion that either the seminal epithelium or the interstitial secretory tissue in the testis are innervated directly. Neither do physiological data indicate that the secretory activity of these tissues is subject to nervous influences except as it is affected by vasomotor changes. On the other hand, psychic influences play an important rôle in the control of the organs directly involved in the sexual act. It has, therefore, been assumed by some that the sex organs are represented in the cerebral cortex. Doubtless, this is true of the striated musculature involved, but, as pointed out above, the discharge of seminal fluid cannot be called forth as a purely voluntary act. There is no conclusive evidence, therefore, that the smooth musculature involved either in the process of erection or the act of ejaculation receives direct cortical impulses. This musculature responds reflexly to a variety of stimuli arising within the organism as a result of sexual excitation and external stimulation of the penile organ, particularly the glans.

Sexual excitation is a complex phenomenon which depends largely on the functional state of the internal secretory tissue in the sex glands. It cannot be brought about during childhood until the sex glands, particularly the internal secretory tissue, have become functional. If the sex glands are removed early, the development of the seminal vesicles and prostate gland is arrested and sexual excitation can never be achieved. On the other hand, overactivity of the internal secretory function of the sex glands results in a state of sexual hyperexcitability. Here again the functional balance between the sex glands and other endocrin organs plays an important rôle. It may be assumed, therefore, that the psychic functions of the cerebral cortex are influenced by the internal secretions of the sex and endocrin glands and that sexual excitability is determined to a large extent by cortical reactions to these influences. Furthermore, sexual excitability and sexual desire vary with the physiological condition of the sex glands. This is apparent particularly in those species which have a limited mating season. In man, voluntary inhibition also plays an important rôle in sexual excitability and is, under normal conditions, the controlling factor in sexual behavior.

THE FEMALE SEX ORGANS.

Macroscopic Anatomy.—The ovary derives its nerve supply mainly from the ovarian plexus. This plexus arises from the aortic

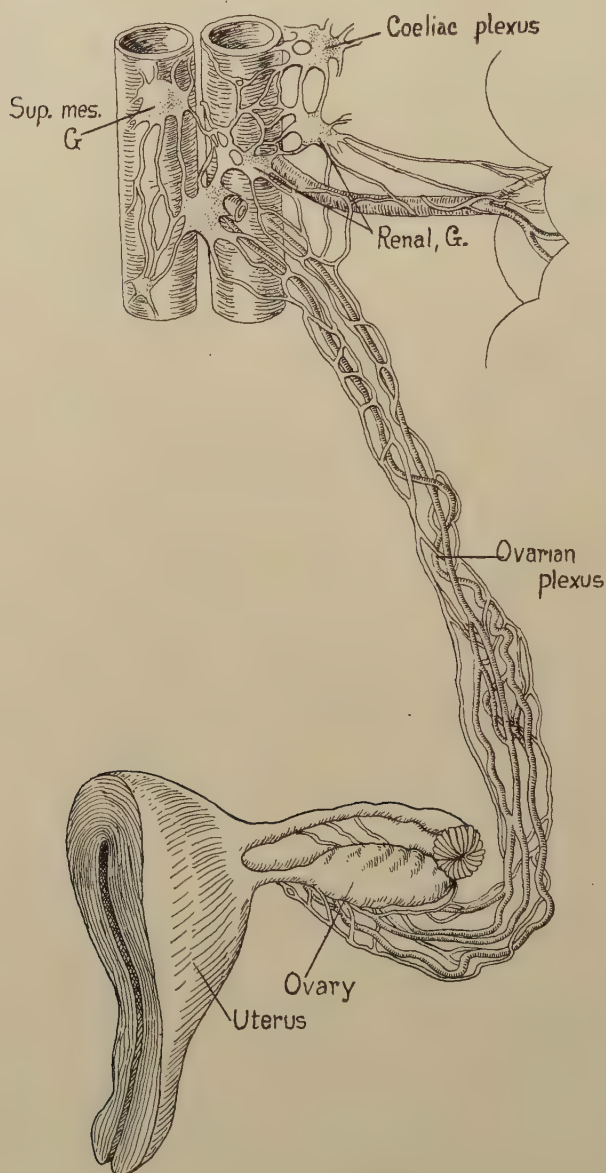


FIG. 53.—Diagrammatic illustration of the innervation of the ovary. (After Dahl.)

and renal plexuses and accompanies the ovarian artery. Many of the fiber bundles which enter the ovarian plexus may be traced directly from the ovarian ganglion located near the origin of the ovarian artery, and the ganglia incorporated in the renal plexus. These ganglia are intimately connected by fibrous rami with the coeliac and superior mesenteric ganglia. The ovarian plexus constitutes a meshwork of nerve fiber bundles which invests both the ovarian artery and vein. It supplies fibers to the Fallopian tube

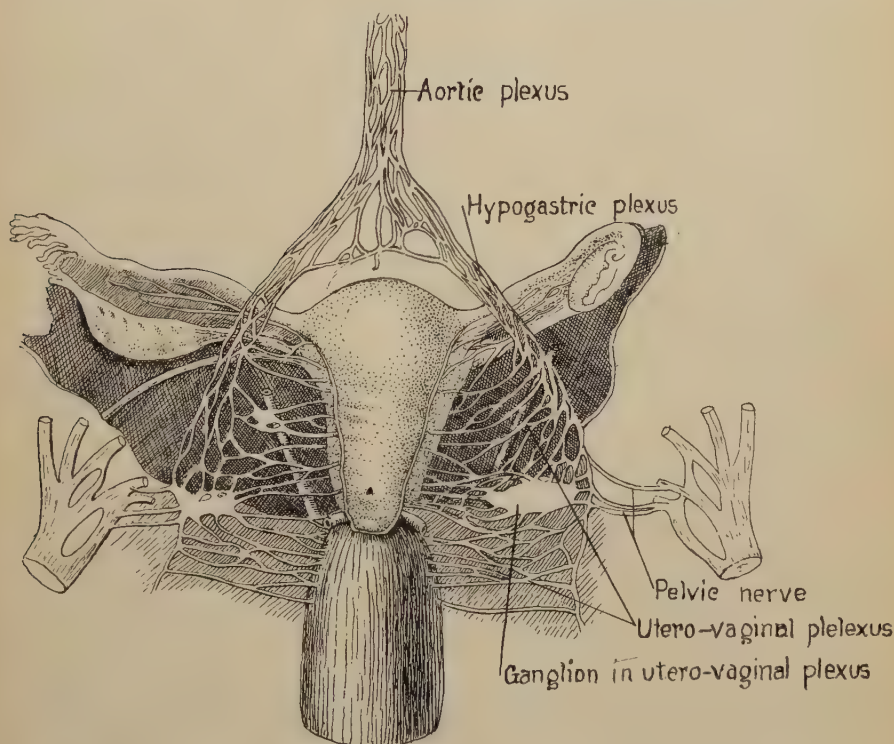


FIG. 54.—Diagrammatic illustration of the extrinsic nerves of the uterus and vagina.
(After Dahl.)

and broad ligament as well as the ovary and communicates, in the broad ligament, with the uterine plexus, through which it also supplies fibers to the uterus. The afferent fibers supplying the ovary are components of the tenth thoracic nerve.

In addition to the fibers derived from the ovarian plexus, the Fallopian tube also receives fibers from the uterine plexus. The afferent fibers supplying the Fallopian tube reach the spinal cord through the eleventh and twelfth thoracic and first lumbar nerves.

The uterus derives its nerve supply mainly from the uterine plexus which is intimately connected with the vaginal plexus and, with the latter, constitutes the utero-vaginal plexus. This plexus corresponds to the prostatic plexus in the male. The utero-vaginal plexus is continuous superiorly with the hypogastric plexus, but also receives fibers directly from the lower lumbar and sacral sympathetic trunk and the second, third, and fourth sacral nerves. Consequently, it includes both sympathetic and parasympathetic components. It also includes a relatively large ganglion, the cervical ganglion, situated about the level of the cervix uteri, and a variable number of smaller ganglia. Afferent fibers are supplied to the uterus through the tenth, eleventh, and twelfth thoracic and first lumbar nerves and also through the second, third, and fourth sacral nerves.

The vaginal plexus is made up mainly of parasympathetic components derived from the sacral parasympathetic outflow, but also contains sympathetic components derived in part from the hypogastric plexus and in part directly from the sacral sympathetic trunk. It supplies fibers to the wall and mucous membrane of the vagina and urethra and gives rise to a cavernous plexus for the clitoris. The clitoris is also supplied by the dorsal nerve of the clitoris which is a branch of the pudendal nerve.

The labia are supplied by both cerebrospinal and autonomic nerves. The cerebrospinal supply of the anterior part of each labium is derived from branches of the ilioinguinal, and that of the posterior part from branches of the pudendal nerve and the perineal branch of the posterior cutaneous nerve of the thigh. The autonomic supply is derived from the vesical and vaginal plexuses.

Microscopic Anatomy.—Intrinsic Innervation of Ovary.—The great majority of the nerve fibers which enter the ovary from the ovarian plexus are unmyelinated and of small caliber. They accompany the ovarian vessels into the stroma, where the larger bundles give rise to branches which accompany the branches of the ovarian vessels. Nerve fibers are supplied to all the ovarian vessels and other smooth muscle in the ovary, but not to the ovarian follicles and interstitial secretory tissue.

Among the early investigators, Frankenhauser (1867), Waldeyer (1870), and Ellischer (1876) described the intrinsic nerves of the ovary as supplying the ovarian follicles as well as the blood vessels. Vedeler (1890) described an abundant nerve supply to the blood vessels in the human ovary, but observed no fibers which enter the follicles. Riese (1891) and Von Herff (1892) both described nerve fibers in the ovary as penetrating the membrana propria and terminating in the stratum granulosum of the follicular wall. Von Herff also described cellular elements in the ovary which he regarded as nerve cells, but which do not correspond to ganglion cells in other

parts of the body. Retzius (1893), deVos (1894), and Mandl (1895) described a nerve supply to the blood vessels in the ovary. They also observed nerve fibers in proximity to the follicles, but could not determine that they either penetrate the follicles or terminate in relation to them. Von Gawronsky (1894) and Winterhalter (1896) described the terminations of nerve fibers in the stratum granulosum of the ovarian follicles. They also described cells which they regarded as ganglion cells within the ovary. Both Von Herff and de Vos (1894) had previously denied the existence of ganglion cells in the ovary. In a later investigation of the nerve supply of the human ovary, Von Herff (1896) was unable to substantiate the claim that ganglion cells occur in the ovary. Neither did Markowitin (1899) observe ganglion cells in the ovary. On the other hand, Bocura (1897) reported isolated ganglion cells in both ovaries of a woman aged fifty-five years, but could determine no essential relationship between these cells and the ovarian nerves. He also described chromaffin cells in the stroma of these ovaries. Abel and McElroy (1912) observed no cells in the ovaries of the dog, cat, and rabbit which they regarded as ganglion cells. According to their observations, the nerves, on entering the ovary at the hilum, become separated into three sets, viz.: a vascular, a follicular, and an interstitial set, all of which anastomose with each other. They described the follicular nerves as lying in the tunicae externa and interna, but not as penetrating the stratum granulosum. Brill (1915) described and illustrated a ganglion in the stroma of the ovary in the mouse and rabbit. He regarded this ganglion as intimately associated with the nerve fiber bundles which enter the ovary. He also described an abundant supply of nerve fibers to the interstitial secretory tissue and traced structures which he regarded as nerve fibers into the corpus luteum to their terminations on lutein cells. He also claimed to have observed nerve fibers in the stratum granulosum of the ovarian follicles. Ramon (1918) described the intrinsic nerves of the ovary as a ganglionated plexus.

Our own studies (Kuntz, 1919), based on pyridine-silver preparations of ovaries of the dog, revealed an abundant nerve supply to the blood vessels and fibromuscular tissue in the stroma, but no nerve fibers which either penetrate the ovarian follicles or terminate in relation to them. Neither did they reveal a nerve supply to the interstitial secretory tissue. Near the periphery of the medulla and in the deeper layers of the cortex many nerve fibers come into close proximity to aggregates of interstitial cells, but careful observation failed to reveal any nerve fibers which terminate in relation to these cells. As nerve-fiber bundles were traced into the cortex, many of them lay in very close proximity to ovarian follicles. Not infrequently a fiber bundle was observed to deviate from its radial course in passing a larger follicle, but no nerve fibers were observed

to penetrate a follicle. Neither were nerve fibers observed in the superficial layers of the cortex except in close proximity to blood vessels. In some instances, nerve fibers appeared to be in the theca folliculi. These must be regarded as nerve fibers which come very close to follicles in their course along peripheral blood vessels. In areas of the cortex in which the interstitial secretory tissue is best developed, nerve fibers are relatively rare. They do not penetrate these areas except as they accompany blood vessels which either supply the interstitial tissue or pass through it. In preparations of ovaries which contained well-developed corpora lutea, a few nerve fibers could, in some instances, be traced along the larger blood vessels in the connective tissue between the columns of lutein cells. None of these fibers were observed to deviate from the blood vessels or to assume a relationship to the lutein cells. Ganglion cells were not observed within the ovary in any of the preparations studied.

Although not a few of the earlier investigators were led to conclude that nerve fibers actually penetrate the ovarian follicles and also supply the interstitial secretory tissue in the ovary, we do not regard the evidence as convincing. Neither do the physiological data available warrant the conclusion that these tissues have a functional nerve supply. The entire efferent nerve supply to the ovary probably is distributed solely to the blood vessels and other structures in the ovary which contain smooth muscle. Ganglion cells have, doubtless, been observed within the ovary in certain cases, but nerve cells do not occur regularly in this organ.

Intrinsic Nerves of the Fallopian Tube.—The Fallopian tube is supplied by both unmyelinated and myelinated fibers derived from the ovarian and uterine plexuses. As the nerve-fiber bundles penetrate the wall of the tube they give rise to branches which are distributed to all the layers except possibly the mucous epithelium. A definite plexiform arrangement of these fiber bundles is not apparent.

Among the older investigators who studied the innervation of the Fallopian tube, Von Herff (1892), Gawrouski (1894), and others supported the theory that nerve fibers penetrate the mucous epithelium and terminate in relation to the epithelial cells. They also claimed to have observed nerve cells in the wall of the tube. These findings are not fully corroborated by the results reported by the majority of the later investigators. Dahl (1916) described nerve fibers in all the layers of the Fallopian tube except the mucous epithelium. He observed very fine branching fibers which approach the epithelium very closely, but could not determine that they actually terminate in relation to the epithelial cells. According to his observations, the nerve supply is most abundant toward the uterine end of the tube. He did not describe a definite plexiform

arrangement of the nerve fibers in any part of the tube. Neither did he observe ganglion cells either in the tube or the broad ligament.

In a recent study of the innervation of the female genitalia of the fowl carried out under my direction, Johnson (1926) described an intramuscular plexus in the oviduct which spreads out between the longitudinal and circular muscle layers. He also observed a plexiform arrangement of nerve fiber bundles in the submucous layer, but a continuous plexus in this layer could not be determined. Fiber bundles could also be traced from the intermuscular plexus into the submucous layer. No nerve fibers were observed to terminate in relation to epithelial cells. Neither were ganglion cells found in the oviduct except near its junction with the cloaca.

Microscopic Structure of the Utero-vaginal Plexus.—The utero-vaginal plexus contains both myelinated and unmyelinated nerve fibers. The cervical ganglion varies greatly in size and compactness. If this ganglion is large and its component ganglion cells are compactly aggregated, there are relatively few small ganglia scattered about in the plexus. If the cervical ganglion is relatively small or contains relatively few ganglion cells arranged in loosely aggregated groups, there is a relatively large number of small ganglia scattered about in the plexus. In a recent study, Blotevogel (1927) proposed the following classification of the ganglia cervicale uteri in the human and various animal species: (1) *Forma compacta*. This is a large compact ganglion which is traversed by all the nerves which join the uterus. Cervical ganglia of this type occur in the mouse, rat, hyena, and sometimes in the human species. (2) *Forma disseminata*. The ganglion complex does not exhibit a single large ganglion, but a small ganglion occurs near the uterus in the course of each nerve joining this organ. This arrangement is observed in the cat, kangaroo, and, in some instances, according to various observers, in the human species. (3) *Forma compacta-disseminata*. Cervical ganglia of this type consist of a large ganglionic mass made up of numerous groups of ganglion cells which are loosely associated with each other. This arrangement occurs in the cat, ape, and, in some instances, in the human species. In all cases in which a large cervical ganglion exists, it is situated on the dorsolateral aspect of the uterus and in proximity to the upper end of the vagina. The neurons in the cervical ganglion and the smaller ganglia in the utero-vaginal plexus are similar morphologically to the ganglion cells in other parts of the autonomic nervous system.

Intrinsic Innervation of the Uterus.—The nerve fibers in the wall of the uterus are distributed mainly to the uterine musculature. Some of the older investigators maintained that nerve fibers also terminate in relation to the uterine mucosa, but the majority of the data available at present do not support this view. According to Dahl (1916), the smaller nerve-fiber bundles, in general, run parallel to

adjacent bundles of muscle fibers to which they give off branches, the fibers of which terminate in relation to muscle cells. He described the nerve supply as fairly uniform throughout the uterine wall, except in the areas adjacent to the Fallopian tubes. Nerve fibers are especially abundant in these areas. He also traced fiber bundles to the mucosa, but observed no nerve fibers in the mucous epithelium.

The majority of the more recent investigators who studied the intrinsic nerves of the uterus also emphasized the abundance of nerve fibers in the uterine musculature and along the blood vessels. Certain of them traced nerve fibers into the uterine mucosa and claimed to have observed nerve-fiber terminations in relation to this epithelium. Others were unable to observe nerve fibers which actually reached the mucous epithelium. The data bearing on the relation of nerve fibers to the uterine glands are relatively meager. In view of the fact that so many among the more recent investigators failed to observe nerve fibers in connection with the mucous epithelium, and in view of the profound degenerative and regenerative changes which take place in the uterine mucosa, we must regard the existence of nerve-fiber terminations in the uterine mucosa as extremely doubtful.

Certain investigators described elements in the wall of the uterus in the human and animal species which they interpreted as ganglion cells; others found no ganglion cells within the uterine wall. Medowar (1928) stated definitely that he could find no intramural ganglion cells in the uterus of the dog. In not a few instances, the elements which were described as ganglion cells in the wall of the uterus were dissimilar to ganglion cells in other parts of the autonomic nervous system. They probably were not cells of nervous origin. True ganglion cells probably were observed in the wall of the uterus in some instances. These must be regarded as cells which became displaced from the ganglia in the utero-vaginal plexus during the course of development. The weight of evidence available at present does not warrant the conclusion that ganglion cells occur regularly in the uterine wall.

Intrinsic Innervation of the Vagina.—The great majority of the nerves which join the vagina from the utero-vaginal plexus enter its upper and middle parts. No nerves of macroscopic size can be traced from this plexus to the lower part of the vagina. The intrinsic nerves of the vagina form a plexiform meshwork which includes numerous small ganglia.

According to Gawrouski (1894), some of the vaginal nerves extend through the muscularis into the mucosa and terminate in the vaginal epithelium. Some of the older investigators also described end organs similar to Pacinian corpuscles in the vaginal mucosa.

Nearly all the more recent investigators, including Jung (1905),

Dahl (1916), and Medowar (1928), who studied the intrinsic nerves of the vagina described a relatively simple plexiform arrangement of nerves which includes small ganglia in the upper and middle parts of the vagina. According to Dahl, the neurons in these ganglia are morphologically identical with those in the uterovaginal plexus. He found no ganglion cells in the lower part of the vagina. Neither did he find ganglion cells in the inner layers of the muscularis or in the connective tissue between the muscularis and the vaginal epithelium. He was also unable to find end organs of any kind in the vaginal mucosa.

Innervation of the External Genitalia.—Sensory end organs in the female external genitalia were observed by not a few of the older anatomists. On the basis of the earlier accounts of these organs and the results of his own histological studies, Dahl (1918) advanced the opinion that the various morphological types of sensory end organs in the female external genitalia possess certain common characteristics. Although they vary in form and structure, the arrangement of the terminal portions of the nerve fibers with which they are connected is quite uniform. He, therefore, proposed that they be regarded collectively as genital sense organs. He found these organs present in abundance in the clitoris and labia minora, but was unable to find them in the labia majora. He also pointed out that they are situated more superficially in the labia minora than in the clitoris. They are much more abundant in the clitoris than in the labia minora. Furthermore, they are more abundant in the clitoris in the deeper than in the superficial layers. In general, the genital sense organs are separated from the surrounding tissue by connective-tissue capsules. The afferent nerve fibers which terminate in these end organs are myelinated components of the nerve of the clitoris and reach the spinal cord through the pudendal nerve.

In addition to the myelinated fibers which terminate in the genital sense organs, the external genitalia are also supplied by unmyelinated nerve fibers. Some of these fibers lie close to the epidermis, but the majority of them obviously are related to the blood vessels. The unmyelinated nerve fibers in the clitoris and labia minora are derived mainly from the cavernous plexus of the clitoris.

Nervous Influences in the Functioning of the Female Sex Organs.

—The older literature bearing on the rôle of the nervous system in the regulatory control of the female sex organs is exceedingly abundant and replete with conflicting data and conclusions which, in the light of present knowledge, obviously are erroneous. A comprehensive review of this literature in this connection could serve no useful purpose; therefore, an attempt will be made to state the main facts regarding the rôle of nervous influences in the functional control of the female sex organs with only such references to the literature as may be necessary to indicate the experimental back-

ground of the current physiological conceptions regarding the functional innervation of the female reproductive system.

Ovary.—Although the ovary is abundantly supplied by nerve fibers, the distribution of these fibers seems to be limited to the blood vessels and the fibromuscular tissue in the stroma. There is no conclusive evidence for the direct functional innervation of either the ovarian follicles or the interstitial secretory tissue. It cannot be assumed, therefore, that the ovarian functions are subject to direct nervous regulation. They are, doubtless, influenced by vasomotor changes in the ovary which are mediated through the ovarian plexus and the nerves arising from it which innervate the ovarian blood vessels.

Uterus and Fallopian Tubes.—The sympathetic nerves supplying the uterus and Fallopian tubes exert a motor influence; the parasympathetic nerves, an inhibitory influence. Furthermore, the sympathetic supply includes the vasoconstrictor and the parasympathetic supply the vasodilator fibers for the female genitalia. Consequently, the sympathetic and parasympathetic nerves respectively exhibit essentially the same functional relationships in the female as in the male sex organs. The effect of stimulation of these nerves, however, is in general less marked in the female than in the male.

In general, stimulation of the hypogastric nerves exerts a motor effect on the uterus and Fallopian tubes, although, according to some, this effect is very slight. It is also quite generally conceded that afferent fibers supplying the uterus and Fallopian tubes traverse the hypogastric plexus. Stimulation of the pelvic nerve in general elicits inhibition of the uterus and dilatation of the blood vessels, particularly of the clitoris. In spite of the fact that certain investigators claimed to have observed contraction of the uterus in response to parasympathetic stimulation, it must be admitted that the effect of these nerves on the uterus is, in general, inhibitory. That the parasympathetic nerves contain vasodilator fibers is generally conceded. The pelvic nerve also includes afferent fibers which supply the external genitalia.

Genital Reflexes.—The spinal centers involved in the reflex control of the sex organs in the female, as in the male, are located in the sacral and upper lumbar regions of the spinal cord. The anatomical relationships of these centers and the afferent and efferent nerves involved are essentially identical in both sexes. The physiological relationships are also comparable. Stimuli arising within the uterus, Fallopian tubes, or Bartholin's glands may elicit reflex contraction of the smooth musculature of the genital tract through the lumbar center. Stimulation of the sensory end organs in the clitoris elicits reflexes through the sacral center which bring about vasodilatation and turgor of the erectile tissue in the clitoris. This reaction is

comparable to erection in the male. Summation of the sensory impulses arising in the external genitalia also results in a discharge of efferent impulses from the upper lumbar center which brings about expulsion of the accumulated secretion of Bartholin's glands. This reaction is comparable to the expulsion of seminal fluid in the male. In like manner, the summation of impulses arising in the external genitalia may result in the discharge of efferent impulses from the upper lumbar center through the hypogastric and uterine plexuses, which result in peristaltic contraction of the uterine musculature and expulsion of mucus from the cavity of the uterus. These phenomena are associated with the sexual orgasm.

The Sexual Orgasm.—The reactions involved in the sexual orgasm in the female are less definitely known than those involved in the corresponding phenomenon in the male. According to Dahl (1916), the sexual orgasm involves comparable reactions in both sexes. He assumed that the afferent impulses which give rise to the sensations involved arise in the female, as in the male, in consequence of the contraction of the smooth musculature of the genital tract. Peristaltic contractions are normally initiated in the Fallopian tubes when sexual excitation is at its height. These contractions are propagated to the uterus and vagina and are followed by rhythmic contractions of the striated sphincter vaginae muscles. They are comparable to those in the male which, according to current conceptions, give rise to the afferent impulses involved in the sexual orgasm.

Reflex and Automatic Reactions of the Uterus.—It was not unknown to Hippocrates that stimulation of the mammary gland elicits uterine contractions which may give rise to painful sensations. Uterine contractions in response to stimulation of the breasts become more pronounced near the termination of pregnancy. Reflex reactions of the female genitalia may also be elicited by direct stimulation of any afferent nerve.

Spontaneous contraction of the musculature of the uterus in the absence of extrinsic nervous influences has been observed by not a few investigators. By means of kymographic records of the spontaneous contractions of excised pieces of the uterus and vagina of the rabbit, Kehrer (1907) was able to show that the spontaneous movements differ in the various parts of these organs. He observed regular pendulum movements in the horns of the uterus. The cervical musculature was less active, but its contractions were more intensive. The vaginal musculature was only slightly active. Holste (1923) also published kymographic records of the rhythmic spontaneous contractions of the musculature of the excised uterus of the guinea-pig. He emphasized the high degree of automaticity of this musculature.

Rein (1902) reported the spontaneous birth of young in the rabbit

following section of all extrinsic nerves to the uterus. Spontaneous parturition following paralysis of the lower half of the body by reason of lesions or transection of the spinal cord has also been reported by other investigators. Such spontaneous parturition proceeds with abnormal rapidity. The contractions of the uterus seem to be more powerful than under conditions of normal innervation. This fact suggests that under normal conditions nervous inhibition also plays an important rôle in uterine activity (Zimmerman, 1914; Schmidt, 1915). The fact that tonus-stimulating drugs produce a more marked effect on the uterine musculature following section of the extrinsic uterine nerves than under conditions of normal innervation also supports this theory.

In view of the experimental data available at present, it may be assumed that the uterine musculature, like other smooth muscle, possesses the inherent capacity to undergo rhythmic contractions, but under conditions of normal innervation the activity of this musculature is subject to both motor and inhibitory nervous influences which may be of reflex or central nervous origin.

CHAPTER XIV

INVOLUNTARY INNERVATION OF THE EYE.

EXTRINSIC NERVES OF THE EYE.

THE eye is supplied by sympathetic, parasympathetic, and sensory fibers which reach it through the ciliary nerves. The short ciliary nerves arise from the ciliary ganglion. These nerves also convey sympathetic fibers to the orbital muscle. The long ciliary nerves arise from the nasociliary branch of the ophthalmic nerve. The smooth muscle in the eye-lids (tarsal muscles) is supplied by sympathetic fibers which traverse the voluntary nerves to these organs. The sympathetic fibers in question are derived from the superior cervical sympathetic ganglion through the internal carotid and cavernous plexuses; the parasympathetic fibers arise in the ciliary ganglion. The afferent fibers supplying the sensory innervation of the eye are derived from the nasociliary branch of the ophthalmic nerve.

The preganglionic fibers to the ciliary ganglion arise in the mid-brain, in a special group of visceral efferent neurons, the Edinger-Westphal nucleus, which is associated with the motor nucleus of the oculomotor nerve. They traverse the oculomotor nerve, the inferior division of which gives rise to the short motor root through which they reach the ciliary ganglion. The sympathetic fibers which traverse the ciliary ganglion are derived directly from the cavernous plexus on the internal carotid artery through a slender ramus which either reaches the ganglion as an independent sympathetic root or becomes incorporated in the long root which connects the ciliary ganglion with the nasociliary branch of the ophthalmic nerve and conveys the sensory fibers which traverse the ciliary ganglion to be distributed through the short ciliary nerves. The preganglionic fibers involved in the sympathetic innervation of the eye arise in the upper thoracic segments of the spinal cord. By stimulation experiments, Langley (1897) determined that the preganglionic fibers involved in the innervation of the dilator pupillæ muscles leave the spinal cord in the upper three thoracic nerves. Stimulation of the lower cervical nerve in the cat, in his experiments, did not elicit pupillary dilatation. Neither did stimulation of the fourth thoracic nerve. Stimulation of the first three thoracic nerves regularly elicits dilatation of the pupil. The great majority of these fibers run in the first and second thoracic nerves.

Stimulation of the third thoracic nerve alone commonly elicits only a very slight pupillary reaction. The postganglionic sympathetic fibers which supply the dilator pupillæ muscle do not follow the course of the internal carotid artery all the way to the cavernous plexus. As early as 1878 François-Frank observed, in the dog, that the pupil dilates in response to stimulation of the sympathetic fibers which pass through the middle ear. It is also known that destruction of the mucosa of the middle ear and the base of the foramen rotundum abolishes pupillary reactions elicited by stimulation of the cervical sympathetic trunk. The results of Dieter's (1927) recent studies indicate clearly that the sympathetic oculo-pupillary fibers pass through the middle ear (on the promontory)



FIG. 55.—Diagram illustrating the autonomic innervation of the eye. Dotted lines indicate sympathetic, and dashed lines indicate parasympathetic fibers. *C.G.*, ciliary ganglion; *C.M.*, ciliary muscle; *G.C.*, geniculate ganglion; *G.S.P.N.*, greater superficial petrosal nerve; *L.C.N.*, long ciliary nerve; *L.G.*, lacrimal gland; *L.N.*, lacrimal nerve; *Max.N.*, maxillary nerve; *M.M.*, muscle of Miller; *N.III*, oculomotor nerve; *N.V.*, trigeminal nerve; *N.VII*, facial nerve; *Oph.G.*, ophthalmic artery; *Opt.N.*, ophthalmic nerve; *S.C.N.*, short ciliary nerves; *Sp.G.*, sphenopalatine ganglion.

in man as well as in the dog, cat, and rabbit. The exact course of these fibers has been determined by the combined physiological, anatomical, and embryological studies of many investigators. After leaving the superior cervical sympathetic ganglion they follow the internal carotid artery for a short distance, and then deviate into the middle ear with the carotico-tympanic fibers. Leaving the middle ear they pass through the base of the cranium lateral to the nerve in the pterygoid canal and become associated with the cavernous plexus. The majority of the postganglionic sympathetic fibers to the eye do not actually pass through the ciliary ganglion. Some of them reach the eye through the long ciliary nerves; others traverse the sympathetic root of the ciliary ganglion and become incorporated

in the short ciliary nerves just distal to the ganglion. In no case do they enter into functional relationship with neurons in the ciliary ganglion. The long ciliary nerves do not communicate with the ciliary ganglion, but pass directly to the eyeball. In general, these nerves include two groups of fibers, viz.: those which traverse the nasociliary nerve, including mainly afferent fibers for the sensory innervation of the eye, and those which are derived directly from the plexus on the ophthalmic artery. The fibers which innervate the dilator pupillæ muscles belong to the latter group.

According to Margitot and Bailliart (1926, 1927), the eye also receives efferent fibers, probably vasodilators, which traverse the trigeminal nerve. Rochat (1926) also reported the results of experiments involving section of the cervical sympathetic trunk and oculomotor nerve and stimulation of the trigeminal nerve in decerebrated rabbits which led him to conclude that the eye receives efferent fibers via the trigeminal nerve which traverse the semilunar and ciliary ganglia. These findings are contrary to the current teaching and await further confirmation.

INTRINSIC NERVES OF THE EYE.

The short ciliary nerves, fifteen or more in number, arise from the ciliary ganglion and pass to the eyeball. They convey postganglionic parasympathetic fibers which arise in the ciliary ganglion, and sympathetic and sensory fibers which join this ganglion through its sympathetic and sensory roots. The short ciliary nerves penetrate the sclera and chorioid to be distributed to the various parts of the eye. In the sclera, nerve fibers are present between the fibrous bundles. Their exact mode of termination is unknown. The cornea is richly supplied by sensory fibers which form an annular plexus around its periphery. Fibers pass from this plexus into the cornea and ramify in the substantia propria, forming the fundamental or stroma plexus, from which fibers penetrate the elastic lamina and form a subepithelial plexus which gives off delicate fibers which ramify between the epithelial cells. Some of these fibers extend out into the superficial layers. Fibers arising from the annular and stroma plexuses extend into the substantia propria and come into close relation to the corneal cells. The choroid and iris are supplied by fibers derived from both the long and short ciliary nerves. These fibers traverse the perichoroidal lymph space, where they form a plexus from which fibers are supplied to the choroidal blood vessels. A second plexus is formed in front of the ciliary muscle from which fibers are supplied to the ciliary muscle and iris. Ganglion cells have been described in both these plexuses. On the basis of the results of the more recent anatomical studies, the existence of ganglion cells in the iris seems highly improbable.

Balado (1927) was unable to detect any nerve cells in this structure, although he studied both methylene blue and silver preparations. The nerve fibers in the iris extend as far as its pupillary margin and supply its muscle fibers and blood vessels. The fibers which supply the sphincter pupillæ and ciliary muscles are of parasympathetic, and those which supply the dilator pupillæ and the muscles which control the nictitating membrane are of sympathetic origin.

THE CILIARY GANGLION.

In the foregoing anatomical consideration, the ciliary ganglion is regarded as purely parasympathetic. The classification of this ganglion has, however, long been a matter of controversy. Neither is there at present general agreement regarding its exact anatomical and physiological relationships. Among the older investigators, Arnold (1831) and Rauber (1872) assigned the ciliary ganglion to the autonomic system. Reichart (1875) first described bipolar cells in this ganglion. Schwalbe (1879), after extensive anatomical studies embracing all classes of vertebrates, concluded that the ciliary ganglion belongs to the cerebrospinal series and represents the sensory root ganglion of the oculomotor nerve. Van Gehuchten (1893), although he studied Golgi preparations of the ciliary ganglion in man, also regarded it as a sensory root ganglion. Although Krause (1882) regarded the ciliary ganglion as homologous with the spinal ganglia in the lower vertebrates, he advanced the opinion that it is a mixed ganglion in mammals, being made up in part of cerebrospinal and in part of autonomic ganglion cells. Burkheimer (1897) and Fritz (1899) also regarded the ciliary ganglion as a mixed ganglion. Holtzmann (1896), who studied the ciliary ganglion in various vertebrates, pointed out the possibility that it may differ in character in different vertebrate types. He regarded it as purely cerebrospinal in Amphibia and birds. In the dog, he found ganglion cells of both cerebrospinal and autonomic character, but in the cat, only cells of autonomic character in the ciliary ganglion. Marina (1901), who studied the ciliary ganglion in man, suggested that it might be regarded as intermediate between the cerebrospinal and autonomic ganglia. He also regarded it as a mixed ganglion. Onodi (1904), on the basis of studies carried out in elasmobranchs, expressed the opinion that all the ganglia in the head include both cerebrospinal and autonomic ganglion cells. Carpenter (1911) also observed ganglion cells in the ciliary ganglion in birds which differ morphologically from the usual autonomic types. He regarded this ganglion "as a purely motor ganglion, with peculiar histological characters, belonging to the mid-brain and bulbar divisions of the autonomic nervous system."

Retzius (1894) and Michel (1894) found only multipolar neurons in the ciliary ganglion and regarded it as a purely autonomic structure. Likewise, Marinesco, Parhon, and Goldstein (1908), who studied the ciliary ganglion in various mammals, including apes and man, found only multipolar neurons in this ganglion. Sala (1910) and Müller and Dahl (1910), who studied this ganglion intensively in man, also found only multipolar ganglion cells. All of these investigators regarded the ciliary ganglion as a purely autonomic (parasympathetic) structure.

In a recent exhaustive study of the ciliary ganglion in man, Pines (1927) described ganglion cells of eight morphological types. While the great majority of these cells are multipolar, he also described bipolar and unipolar cells. The single process of the unipolar cell commonly bifurcates in the manner of the single process of a spinal ganglion cell. Among the multipolar cells, he also described cells which he identified with the cells of Golgi's second type. They are characterized by a short axon which does not reach out to a peripheral organ, but terminates in relation to a neighboring cell in the ciliary ganglion. Pines advanced the opinion that relationships of this kind serve to transmit impulses from one neuron to another within the ganglion. He also described the terminations on ganglion cell bodies in the ciliary ganglion of collaterals which arise near the base of axons which extend peripherally in the ciliary nerves. The existence of ganglion cells of these two types within the same ganglion shows quite clearly that Langley's conception according to which all autonomic neurons constitute peripheral links in visceral efferent chains is inadequate to explain all the existing anatomical relationships in the autonomic ganglia. If Pines' observations are confirmed, the existence of intercalated or association neurons and reflex connections in the ciliary ganglion in man must be conceded in spite of the general acceptance of Langley's theory.

The data obtained by Pines show that the ciliary ganglion in man is a relatively complex structure. The majority of the ganglion cells, doubtless, are multipolar parasympathetic neurons whose functions are essentially motor. Certain of the cell types described by Pines do not lend themselves to this interpretation. Pines regards the neurons which resemble spinal ganglion cells as receptive in function and suggested that those whose axons do not extend beyond the border of the ganglion, but terminate on the cell bodies of neighboring ganglion cells may serve to complete reflex arcs which do not traverse the central nervous system. According to this view, the ciliary ganglion is not purely motor in function, but constitutes an independent reflex center.

THE RÔLE OF THE CERVICAL SYMPATHETIC IN THE FUNCTIONAL CONTROL OF THE EYE.

That section of the cervical sympathetic trunk or extirpation of the superior cervical sympathetic ganglion results in certain definite ocular changes is well known. Purfour and Petit (1772) were not unfamiliar with these phenomena. Following section of the cervical sympathetic trunk in the cat, they observed that the eye was somewhat sunken, the rima oculi narrow, the pupil constricted, the nictitating membrane extended, and the vessels of the conjunctiva dilated. Their observations were later corroborated by those of other investigators. These ocular changes are now familiar clinical phenomena following cervical sympathectomy in man.

Budge (1855), who studied the pupillary reactions under various experimental conditions, observed that the dilator pupillæ muscles were atonic following section of the cervical sympathetic trunk. He concluded, therefore, that this operation breaks the dilator fibers. He first determined that these fibers emerge from the spinal cord in the upper thoracic segments. He concluded that this portion of the spinal cord includes a center for pupillary reactions, and designated it the cilio-spinal center.

That a true cilio-spinal center exists in the upper thoracic segments of the spinal cord has been maintained by some of the more recent investigators and denied by others. Langendorff (1909) advanced experimental data which he interpreted as demonstrating the existence of a center in the upper thoracic cord which exerts a tonic influence on the dilator pupillæ muscle. In his experiments, section of the cervical sympathetic trunk, following section of the spinal cord in the upper cervical region, resulted in constriction of the pupil. Lateral hemisection of the cervical spinal cord in the rabbit was followed by temporary constriction of the corresponding pupil, but if the cervical sympathetic trunk also was cut, the pupillary constriction remained permanent. According to Langendorff, these results can only be explained by assuming the existence of a cilio-spinal center in the upper thoracic segments of the spinal cord. Karplus and Kreidl (1911) did not admit that the data advanced by Langendorff prove the existence of a cilio-spinal center. They maintained that if, as observed in their own experiments (1909), unilateral stimulation of the cervical spinal cord elicits bilateral pupillary dilatation, the effect of section of the cervical sympathetic trunk on the dilator pupillæ muscle must necessarily differ from the effect of unilateral section of the cervical spinal cord. They did not regard it necessary to assume the existence of a cilio-spinal center in order to explain the observed

pupillary phenomena. On the other hand, they have shown that stimulation of the sympathetic center in the diencephalon results in bilateral pupillary dilatation, and that the fiber tracts through which impulses from this center are conveyed to the cervical sympathetic in the cat remain uncrossed in the cervical spinal cord. It must be assumed, therefore, that the impulses which reach the cervical sympathetic on the opposite side are conveyed by commissural fibers in the upper thoracic segments of the spinal cord.

That dilatation of the pupil, separation of the eye-lids, and retraction of the nictitating membrane may be brought about, in experimental animals, by stimulation of the cerebral cortex has long been known. It need not be assumed, however, that the smooth musculature of the eye and other orbital structures are directly represented in the cortex. Braunstein (1894) attempted to explain pupillary dilatation following cortical stimulation as a result of relaxation of the sphincter pupillæ due to inhibition of the pupillary center in the oculomotor nucleus. Karplus and Kreidl (1911) did not admit the validity of this explanation. In their experiments, the pupil not infrequently failed to dilate in response to stimulation of the cortex or the autonomic center in the diencephalon following section of the cervical sympathetic trunk. They also pointed out that, following section of the cervical sympathetic trunk, dilatation of the pupil in response to stimulation of the sciatic nerve is not accompanied by separation of the eye-lids and retraction of the nictitating membrane. Furthermore, they produced reflex dilatation of the pupil following section of the oculomotor nerve, although the pupil was already dilated. That cortical stimulation may, at least under certain conditions, result in relaxation of the sphincter pupillæ muscle and consequent dilatation of the pupil cannot be denied. On the other hand, the experimental data advanced by Karplus and Kreidl show clearly that active pupillary dilatation may be elicited by cortical stimulation and that the efferent impulses are conveyed through the cervical sympathetic. Their experimental data also prove that the cortical impulses in question are mediated through the sympathetic center in the diencephalon and that they are conveyed by the same pathways in the spinal cord as impulses arising from direct stimulation of the diencephalic center. Destruction of the hypothalamus on one side prevents the conduction of impulses from the frontal cortex on the same side to the cervical sympathetic, but does not influence the effect on the cervical sympathetic of stimulation of the frontal cortex of the opposite side. As stated above, the descending paths from the diencephalic center are uncrossed, but the impulses are carried out to both cervical sympathetic trunks through the upper thoracic nerves.

THE PARASYMPATHETIC CONTROL OF OCULAR FUNCTIONS.

Stimulation of the oculomotor nerve brings about constriction of the pupil by reason of active contraction of the constrictor pupillæ. On the other hand, section of the oculomotor nerve is followed by dilatation of the pupil by reason of the absence of tonus in the sphincter in the presence of normal tonus in the dilator pupillæ muscle. Sympathetic stimulation, following section of the oculomotor nerve, brings about still further pupillary dilatation by reason of active contraction of the dilator pupillæ muscle.

The light reflex involves mainly the parasympathetic innervation of the muscles of the iris. The accommodation reflex involves also the innervation of the ciliary muscle. The sympathetic innervation of the iris plays a part in these pupillary reactions only by reason of its tonic influence on the dilator pupillæ muscle. When the ciliary muscle contracts to accommodate the eye for a near object, the sphincter pupillæ contracts simultaneously, whereby the pupil is constricted. This is the accommodation reflex as it is commonly understood. In reality it is an associated movement in which the act of accommodation carries with it the constriction of the pupil, probably by reason of the fact that the efferent discharge of the cells in the mid-brain which control the ciliary muscle also affects the cells which control the sphincter pupillæ. The accommodation reflex also involves the associated activity of the extrinsic muscles of the eye. Under normal conditions, every act of accommodation for near vision is accompanied not only by constriction of the pupil, but also by convergence of the eyeballs, due to bilateral contraction of the medial rectus muscle.

The light reflex is brought about by light entering the eye. That the pupil dilates in darkness or dim light and contracts to a pin-point when the retina is strongly illuminated are facts of common experience. The functional value of this reflex is obvious. Enlargement of the pupil in dim light increases the total illumination of the retina, thereby increasing visual power; constriction of the pupil in strong light also aids vision by decreasing the illumination of the retina and diminishing spherical aberration. The effective stimulus which brings about this reflex is the light falling on the retina; the afferent fibers involved traverse the optic nerve. Inasmuch as part of the optic nerve fibers cross in the optic chiasma, the light reflex involves both eyes. The efferent fibers involved are preganglionic components of the oculomotor nerve and postganglionic neurons in the ciliary ganglion. The central connections are not fully known, although it is generally assumed that the afferent fibers in question terminate in the superior colliculus and that the impulses are transferred to the Edinger-Westphal nucleus by means of intercalated neurons. Injury to either the afferent or efferent

path diminishes or destroys the reflex. It is also lost in some cases in which neither of these paths seems to be injured. For example, in *tabes dorsalis* and *general paresis*, the pupil is constricted and does not react to light (*Argyll-Robertson pupil*), but the accommodation reflex remains intact. This phenomenon suggests that the central connections involved in the light reflex differ from those involved in the accommodation reflex. The explanation of this difference awaits further investigation. It is quite generally assumed that the reflex reaction of the sphincter pupillæ to light is greatest when the retina is stimulated at or near the fovea and that it varies directly with the intensity of the light and the area illuminated (Abelsdorff and Feilchenfell, 1904).

SYNERGIC ACTION OF SPHINCTER AND DILATOR PUPILLÆ.

Under normal conditions, the sphincter and dilator muscles of the iris seems to be kept in a state of tonic activity by impulses received through their respective motor fibers. They constitute a synergic mechanism which responds promptly and smoothly to an excess of stimulation of either set of nerves. The synergic action of these muscles is, at least in a measure, comparable to that of the flexor and extensor muscles around a joint. The explanation of specific pupillary reactions is complicated, however, by the fact that dilatation of the pupil may be brought about either by contraction of the dilator muscle or relaxation (inhibition) of the sphincter, while constriction of the pupil may be brought about either by contraction of the sphincter or relaxation of the dilator muscle. On the other hand, the contraction of one of these muscles may always be accompanied by inhibition of the other, as is assumed to be the case with the flexor and extensor muscles of the limbs. Certain experimental data strongly suggest that dilatation of the pupil may normally be brought about by a double action of this sort, *i. e.*, contraction of the dilator muscle followed by inhibition of the sphincter (Anderson, 1903). Alterations in the size of the pupil occur not only in response to the effect of light on the retina and in the accommodation reaction, but also under a variety of other conditions both normal and pathological. In sleep the pupils are constricted and the eyes rotate upward and outward. Pupillary constriction may, in this case, be due to inhibition of the tonus of the dilator muscle or increased tonicity of the sphincter. The assumption that the tonicity of the sphincter pupillæ is increased during sleep is favored by the fact that experimental data are not wanting which indicate that during the waking state the mid-brain center which controls the sphincter pupillæ is kept in a state of inhibition by a constant influx of sensory impulses. These

inhibitory impulses are, in a large measure, cut off during sleep; consequently, the sphincter tonus is increased. Emotional states are also accompanied by changes in the size of the pupil which aid in producing the facial expressions characteristic of these conditions. For example, deep emotions of pleasure as well as fear are commonly accompanied by pupillary dilatation. This reaction may be explained either as the result of stimulation of the dilator muscle or inhibition of the tonus of the sphincter. In favor of the former explanation is the fact that strong emotional states are accompanied by general sympathetic stimulation. As was pointed out by Ingalls (1923), this psychic or emotional mydriasis is closely allied to the typical reflex contraction of the dilator pupillæ muscle ordinarily elicited by cutaneous stimulation. Like many other effectors which are innervated through the autonomic system, this muscle responds to all manner of psychic changes as well as to a great variety of sensory stimuli. On the other hand, it is not inconceivable that the same afferent impulses which give rise to the emotional state also inhibit the pupillary center in the mid-brain.

The ciliary muscle also responds reflexly to a variety of afferent impulses. Percy and Allen (1927) reported reduction of 2 to 5 diopters in accommodation in human subjects in response to increased internal pressure by means of a balloon in the stomach or lower part of the colon. The fundus veins were also enlarged and after fifteen to twenty minutes the retina became edematous.

RELATIVE IMPORTANCE OF THE SPHINCTER AND DILATOR MECHANISMS.

Although the sphincter and dilator pupillæ muscles sustain the relation of synergists to each other, the former must be regarded as of much greater functional importance than the latter. The dilator pupillæ muscle is closely related functionally to other visceral structures which are innervated through the thoracolumbar autonomic outflow. The sphincter pupillæ is more highly specialized than the dilator both structurally and functionally and is strictly a part of the visual organ. The dilator pupillæ is not essential for vision, although it may play a minor rôle in the visual functions of the eye. Unlike the sphincter, it is extremely sensitive, at least in the higher vertebrates, to stimuli which elicit general sympathetic reactions. It may, therefore, be classified with other visceral effectors innervated through the autonomic system which are highly sensitive to afferent impulses and, in the higher vertebrates, to cortical influences. Whatever effect it has on the accommodation and light reflexes is exerted mainly by virtue of the tonus which is constantly maintained in it through its sympathetic innervation.

Both these muscles are of epithelial origin. The sphincter is a stronger muscle than the dilator and contracts more rapidly. In the lower vertebrates, viz.: fishes and Amphibia, the sphincter pupillæ is pigmented and itself reacts to light. In the higher vertebrates, as pointed out above, the light reflex is mediated by a relatively complex reflex mechanism. In man, the light reflex is present at or before birth, while the accommodation reflex does not appear before the fifth month of postnatal life (Ingalls, 1923). That the pupil exhibits considerable variation in size under the same conditions of illumination is well known. Very early and also late in life, the pupil is relatively small. This may be regarded as due to the relatively weak antagonism of the dilator muscle during these phases of life. Albino and blue eyes normally exhibit smaller pupils than dark eyes. This may be regarded as a normal ocular reaction to light. Under ordinary conditions, the ciliary and sphincter muscles usually react together. The pupil may, however, react independently to the amount of light entering it. Consequently, there may be myosis in distant vision under conditions of strong illumination, and mydriasis in near vision under conditions of weak illumination. The dilator pupillæ plays only a secondary rôle in these reactions, which are mainly expressions of tonus changes in the sphincter muscle.

ACTION OF DRUGS ON THE IRIS.

The dilator pupillæ, like other smooth muscle with sympathetic innervation, contracts in the presence of adrenalin. Atropin, homatropin, and cocain exert a mydriatic effect. In animals in which morphin causes excitement, *e. g.*, the cat, it also causes dilatation of the pupil. Physostigmin and pilocarpin are well-known miotics. Regarding the site of the action of these drugs, it may be stated that adrenalin stimulates the sympathetic fiber terminations in the dilator muscle, while atropin paralyzes the parasympathetic fiber terminations in the constrictor muscle. Physostigmin and pilocarpin probably cause miosis by stimulating the endings of the same parasympathetic fibers. Cocain probably first stimulates mainly the endings of the sympathetic fibers in the dilator muscles, and in stronger doses paralyzes the endings of the parasympathetic fibers in the sphincter pupillæ. The stronger mydriatics paralyze the ciliary muscle as well as the sphincter pupillæ, thus destroying the power of accommodation. In the mydriasis of cocain and the miosis of physostigmin, however, the light reflex is not abolished. The stronger miotics stimulate the ciliary muscle; consequently, the eye exhibits a condition of forced accommodation during the period of their activity.

NERVOUS CONTROL OF THE NICTITATING MEMBRANE.

It has been assumed quite generally that the muscles which control the nictitating membrane also receive fibers from the cervical sympathetic and that the path of the postganglionic fibers in question is closely related to that of the fibers which innervate the dilator pupillæ muscle. According to Langley (1900), whose observations were made on cats, dogs, and rabbits, section of the cervical sympathetic trunk results in projection of the nictitating membrane. Slight projection of the nictitating membrane has also been reported following cervical sympathectomy in man.

In certain experiments carried out on cats by De Kleijn and Socin (1915), section of the cervical sympathetic trunk was followed by the characteristic reaction of the nictitating membrane and the eye-lids even after extirpation of the ciliary ganglion and section of both the long and short ciliary nerves and the rectus and oblique muscles with their nerve supply. It must be assumed, therefore, that the fibers which innervate the muscles of the nictitating membrane and the tarsal muscles in the cat neither traverse the ophthalmic nerve nor the short ciliary and eye-muscle nerves, but reach their peripheral destination by some other path which is as yet undetermined (Schilf, 1926).

The sympathetic control of the nictitating membrane, particularly in the rabbit, has long been questioned by certain investigators. Some have even attempted to explain the projection of this membrane as a passive process dependent on the retraction of the eyeball into the orbit (Querido, 1924). Certain physiological findings seem to indicate that, in the rabbit, the trigeminal nerve contains dilator pupillæ fibers. According to Oehl (1874), stimulation of the trigeminal nerve causes dilatation of the pupil, while section of the trigeminal is followed by constriction of the pupil. Mayer (1879) also supported this view. The source of the fibers in question has not been clearly demonstrated. The findings of Vulpian (1874) and Oehl (1874) seemed to indicate quite clearly that they are not derived from the superior cervical ganglion. If the existence of dilator pupillæ fibers in the trigeminal nerve in any animal were satisfactorily demonstrated, it might be assumed that, in the absence of demonstrable sympathetic innervation of the muscle controlling the nictitating membrane, they also are innervated through the trigeminal nerves. The data advanced in support of this view in any specific case are not convincing.

According to Terni (1921, 1922), an accessory nucleus of the abducens which seems to control the muscles of the nictitating membrane exists in reptiles and birds. Furthermore, he presented evidence which seems to demonstrate the existence of a similar accessory nucleus of the abducens in *Mus rattus*. He also cited certain findings

of Van Gehuchten which seem to confirm the existence of this nucleus in the chick, and the work of Lugaro who demonstrated a similar nucleus in the rabbit. Kappers (1922) apparently accepted these findings.

Bucy (1927) pointed out quite clearly that the muscles of the nictitating membrane in the rabbit are not innervated by fibers derived from the superior cervical sympathetic ganglion. He also maintained that the projection of the nictitating membrane is not brought about, in this animal, by retraction of the eyeball and the outward projection of fat. He neither accepts the theory that the muscles of the nictitating membrane in the rabbit are innervated through the trigeminal nerve nor the theory that they are controlled by an accessory nucleus of the abducens, but asserts that "the innervation of the nictitating membrane in the rabbit is as yet undetermined."

In view of the many findings which seem to indicate that in certain experimental animals, especially the cat and dog, the muscles of the nictitating membrane, like the dilator pupillæ, derive their nerve supply from the cervical sympathetic, the rabbit and certain other rodents must be regarded as differing from other mammals in this respect. At any rate, negative findings regarding the effect on the nictitating membrane of the nerves arising from the superior cervical sympathetic ganglion in the rabbit do not warrant the conclusion, in the presence of not a little evidence to the contrary, that the nerves which control the nictitating membrane in other mammals are not derived from the cervical sympathetic.

CHAPTER XV.

AUTONOMIC INNERVATION OF SKELETAL MUSCLE.

ANATOMICAL DATA.

Historical Survey.—The existence in skeletal muscles of unmyelinated nerve fibers of small caliber has long been recognized. As early as 1879 Tschiriew described, in the lizard and adder, unmyelinated nerve fibers of small caliber which terminated in relation to the striated muscle fibers in grape-like structures which he called “*terminaisons en grappe*.” In 1882 Bremer described, in the frog and lizard, fine unmyelinated nerve fibers which enter the end-plates constituting the terminal apparatus of the ordinary motor nerve fibers of striated muscle. He recognized three types of nerve fibers in striated muscle, viz.: (1) coarse myelinated, (2) fine myelinated, and (3) unmyelinated. On the basis of his findings, he concluded that the unmyelinated fibers are connected with the fine, but not with the coarse myelinated fibers. Huber and DeWitt observed fine unmyelinated nerve fibers within the capsules of muscle spindles. They regarded these fibers as sympathetic in origin and probably vasomotor in function. Dogiel (1902) also observed nerve fibers which he regarded as sympathetic in preparations of skeletal muscle, but he did not describe any relationship of these fibers to the muscle fibers.

Perroncito (1901) described and illustrated, in preparations of striated muscle of the lizard, unmyelinated nerve fibers connected with the ordinary motor end-plates, but otherwise distinct from the ordinary myelinated motor fibers. Neither his description nor his illustrations suffice, however, to differentiate these fibers from the unmyelinated ultraterminal filaments, described by Ruffini (1900), which are continuous with the neurofibrillar apparatus of the motor end-plate. In a later paper, Perroncito (1902) described and illustrated fine unmyelinated nerve fibers accompanying myelinated fibers and ending in the same motor end-plates with the terminal branches of the latter. In certain cases, he observed connections of these fine fibers with a perivascular nerve plexus; consequently, he regarded them as sympathetic in origin.

Gemelli (1905) confirmed Perroncito's observations in the main, but maintained that the fine unmyelinated nerve fibers connected with the motor-end plates are continuous with the arborizing terminal filaments of the myelinated fibers. Consequently, he regarded

them as the ultraterminal fibers of Ruffini. Botezat (1906) also described both myelinated and unmyelinated nerve fibers in preparations of skeletal muscles in birds. He pointed out that the terminal structures of the unmyelinated fibers differ from any known sensory terminations and resemble motor endings, but did not otherwise determine the origin or character of these fibers.

Boeke (1909) recognized the existence in striated muscle of a system of fine unmyelinated nerve fibers which seemed to him to be quite independent of the myelinated fibers. He described the terminations of these unmyelinated fibers as end-rings, end-loops, and end-nets. Sometimes he found them imbedded in the sarcoplasm of an ordinary motor end-plate, in other cases they occurred as independent terminations on a muscle fiber. Boeke regarded their hypolemmal position and frequent association with motor end-plates as evidence of their efferent character. He called these terminal structures "accessory" nerve endings, and the unmyelinated fibers connected with them "accessory" fibers.

In a series of later papers, Boeke (1911-1913) discussed this "accessory" system more fully. On the basis of a comparison of his own findings with those of previous investigators who described unmyelinated nerve fibers in skeletal muscles, he concluded that the latter were, in most instances, either unmyelinated collaterals or ultraterminal filaments of ordinary motor fibers, and, therefore, not identical with the accessory system of fibers discovered by him. In 1913 he definitely advanced the opinion that the "accessory" fibers belong to the autonomic nervous system.

Although the morphological data thus far available favored not only the independence of Boeke's "accessory" system of fibers, but also its autonomic origin, the evidence was not fully convincing. The morphological proof of the sympathetic innervation of skeletal muscles rests mainly on Boeke's later experimental anatomical findings. In one series of experiments (1916, 1917) one or another of the nerves supplying the extrinsic muscles of the eye was resected close to its origin from the brain. Three to five days were allowed for the degeneration of the divided fibers, after which the animal was killed and the ocular muscles were prepared for study according to the Bielschowsky method. A careful study of these preparations showed that the medullated nerve fibers and their terminal structures were undergoing degeneration, but the unmyelinated "accessory" fibers with their hypolemmal endings on the muscle fibers remained intact. In Boeke's opinion, these results could only be explained on the hypothesis that the undegenerated unmyelinated nerve fibers reach the eye muscles, via the sympathetic roots of the ciliary ganglion, the fibers of which are derived from the internal carotid plexus. The results of his later experimental studies showed clearly, however, that the conditions which obtain with regard to

the "accessory" innervation of the eye muscles is less simple than this. Preparations of the eye muscles following extirpation of the superior cervical sympathetic ganglion still showed the "accessory" unmyelinated fibers intact, although Boeke recorded the impression that these fibers are less abundant in these preparations than in preparations of the eye muscles on the unoperated side. He concluded, therefore, that the majority of the unmyelinated nerve fibers supplied to the eye muscles belong to the cranial autonomic system.

In a further experimental study, carried out by Boeke and de Barenne (1919), preparations of the intercostal muscles of the cat were examined for intact nerve fibers following degeneration of the spinal nerve fibers in question. Both anterior and posterior roots of the sixth to the ninth thoracic nerves inclusive were resected and the corresponding spinal ganglia extirpated. The animals were killed one month after operation. In order to avoid confusion due to overlapping of the areas of distribution of the intercostal nerves, the muscle tissue to be prepared for study was taken from the seventh intercostal space. Preparations of this tissue showed no intact myelinated nerve fibers nor the motor end-plates associated with them, but fine unmyelinated nerve fibers terminating on muscle fibers by means of delicate end-rings, end-loops, or end-nets were still present. In view of the conditions of the experiments, the conclusion that the unmyelinated fibers in question are sympathetic in origin can hardly be avoided. The description and illustrations of these fibers and their terminations, as published by Boeke and de Barenne, are essentially similar to those of the "accessory" fibers published in Boeke's earlier papers. It is strongly suggested, therefore, that they are identical with the latter and that the so-called accessory fibers are components of the autonomic nervous system. The morphological character and hypolemmal position of the terminal structures of these fibers, as described by Boeke, also strongly suggest that they are efferent in character.

Agduhr (1919), in a similar experimental investigation, examined preparations of certain of the small muscles of the extremities, particularly the interossei, in the cat following degeneration of the spinal nerve fibers. In his experiments, the lower four cervical and first two thoracic nerves were cut distal to the spinal ganglia, leaving the communicating rami intact. The animals were killed five to ten days later. Bielschowsky preparations of the interosseous muscles showed degeneration of the myelinated nerve fibers, both sensory and motor, but a goodly number of unmyelinated fibers remained intact, many of which could be traced to their terminations on muscle fibers. In one set of experiments in which a degeneration time of forty-five days was allowed, the results obtained were essentially identical with those recorded above.

Intact nerve endings were found in the interosseous muscles both hypolemmal and epilemmal in position. Agduhr's findings in general corroborated the earlier findings of Boeke and afforded additional morphological support of the theory that skeletal muscle has a sympathetic nerve supply.

In an experimental study of the innervation of the muscles of the cat's tongue, Langworthy (1924) cut the hypoglossal nerve on both sides. According to his findings, preparations of the tongue muscles, after degeneration of the hypoglossal fibers, showed only a few nerve fibers of small caliber which apparently were associated with the arteries. In methylene-blue preparations of the tongue muscles of the white rat, following degeneration of the hypoglossal nerves, he also found unmyelinated nerve fibers along the arteries and stated that "oftentimes fibers were noted which separated from the arterial root or dipped down from the cutaneous group to enter the musculature. There they ended in fine dust-like nerve endings upon the sarcolemma of the muscle fiber."

Kuntz and Kerper (1924), in a preliminary paper, recorded the results of an experimental anatomical study involving intercostal muscles and the muscles of mastication in the dog. In pyridine-silver and gold-chloride preparations of muscle tissue taken from the eighth intercostal space four weeks after section of both roots of the seventh, eighth, and ninth thoracic nerves distal to the spinal ganglia, leaving the communicating rami intact, and in similar preparations of the muscles of mastication taken twenty-three days after intracranial section of the mandibular nerve, unmyelinated fibers of small caliber were observed in relatively small numbers, some of which could be traced to their terminations on muscle fibers. In view of the advanced stage of degeneration of the myelinated fibers, the conclusion was drawn that the unmyelinated fibers which remained intact are sympathetic in origin. This study was later extended to include muscles of the extremities (Kuntz, 1927). Pyridine-silver preparations of both flexor and extensor muscles, following complete degeneration of the spinal nerve fibers, still show fine unmyelinated fibers, some of which can be traced to their terminations on muscle cells.

Boeke (1927) once more discussed very fully the morphological evidence of the sympathetic innervation of skeletal muscles, reviewing all of his earlier work and adding new experimental data. He was able to verify his earlier findings in all essential details and to supplement them, in many instances, by additional data. On the basis of his own findings and the findings of other recent investigations, particularly those involving degeneration of the cerebrospinal nerve fibers, he concluded that the morphological data available show unmistakably that skeletal muscles are supplied by sympathetic as well as sensory and motor cerebrospinal nerve fibers.

The results of certain other recent histological studies, particularly those of Kulschitsky (1924), Hunter and Latham (1925), Kuré *et al.* (1925), and Garven (1925) also support the theory that skeletal muscles are supplied by fibers of sympathetic origin, but inasmuch as they are based on preparations of normally innervated muscle, they are less convincing than the results of the experimental anatomical studies cited above.

In spite of the volume of anatomical and physiological data on which the conception of the sympathetic innervation of skeletal muscle is based, this conception has not been universally accepted. On the basis of his own findings in preparations of the limb muscles of the frog, Murray (1924) wrote: "Provisionally, then, these fine fibers must be regarded as motor, and as perhaps being branches of the ordinary motor fibers, while remembering that they may possibly belong to the sympathetic supply." More recently, Hinsey (1927) attempted to show that most of the recorded observations which have been interpreted as supporting the theory of the sympathetic innervation of skeletal muscles could quite as well be interpreted in some other way. He suggested that the fine unmyelinated nerve fibers observed in preparations of skeletal muscles following degenerative section of the cerebrospinal nerve fibers may be either unmyelinated branches of sensory or motor fibers which have not undergone degeneration, or regenerating somatic motor fibers. In reporting the results of his own experiments, he stated, "when precaution was used against regeneration and at the same time sufficient time was given for degeneration of the somatic component, no sympathetic fibers ending hypolemmally in skeletal muscle were seen in the small muscles of the foot. . . . We feel that regeneration may account for some of the observations made and recorded in published investigations by Boeke and his followers, where longer degeneration times have been used."

Distribution of Sympathetic Fibers in Skeletal Muscles.—The sympathetic fibers supplying the skeletal muscles, like those supplying the peripheral blood vessels, are conveyed peripherally in the cerebrospinal nerves. In transverse sections of the nerve trunks and their muscular rami, prepared by the pyridine-silver technique, the great majority of the unmyelinated fibers appear aggregated in smaller and larger groups between the myelinated fibers throughout the entire section. Some unmyelinated fibers also occur scattered among the myelinated fibers. In transverse sections of these nerves, following degeneration of the cerebrospinal fibers, the distribution of intact unmyelinated fibers aggregated in groups is essentially identical with the distribution of these fibers in the normal nerves (Fig. 56), but intact unmyelinated fibers not incorporated in these groups were rarely observed in our preparations, following degeneration of the cerebrospinal fibers. Obviously, the

great majority of the sympathetic fibers in the somatic rami of the cerebrospinal nerves are aggregated in larger or smaller bundles. The unmyelinated fibers which occur scattered among the myelinated fibers probably are mainly of cerebrospinal origin.

The terminal branches of the nerves supplying skeletal muscles commonly lie in proximity to the larger blood vessels in the muscles. It is obviously impossible, in preparations of normally innervated muscles, to distinguish between fibers of sympathetic origin and unmyelinated fibers of cerebrospinal origin in all cases. Neither can the abundance of the sympathetic nerve supply to a given muscle be definitely estimated by the abundance of the aggregated unmyelinated fibers in the nerves entering the muscle, since many sympathetic fibers are distributed to the intramuscular blood vessels. The distribution of the sympathetic fibers can best be studied following degeneration of the cerebrospinal fibers. In our experiments, animals subjected to degenerative section of cerebrospinal nerves, leaving the sympathetic fibers intact, showed a wide range of individual variation in the reaction of their tissues to the technique (pyridine-silver) used. Consequently, positive observations regarding the occurrence and distribution of sympathetic fibers in the muscle, following degeneration of the cerebrospinal fibers, depend on the successful impregnation of the unmyelinated fibers and their terminal structures. Failure to observe such fibers in the muscle, even in preparations in which the unmyelinated fibers in the muscular rami of the nerves are impregnated, cannot be regarded as conclusive evidence of their non-existence in the muscle.

As observed in preparations of muscles in which the cerebrospinal nerve fibers have undergone degeneration, the sympathetic fibers, as they approach their terminal distribution, in general, run along the blood vessels. The majority of them lie in close proximity to the smaller vessels, including the capillaries. Many of them enter the vessel walls and terminate there; others deviate from the course of the blood vessels and terminate on striated muscle fibers (Fig. 57, *A*). Only rarely do any of these fibers run more than a short distance independently of the course of a blood vessel. Even in such instances, the relation of the course of the nerve fiber, except that of its terminal portion, to the course of blood vessels is usually apparent. Not uncommonly, particularly if the nerve fibers run singly or in very small bundles, they are so intimately associated with the blood vessels, particularly the capillaries, that they are not easily observed except when they lie alongside the vessels. In some instances, the termination of one of these fibers on a muscle fiber lies close to the vessel along which the nerve fiber took its course. In other instances, the muscle fiber on which the nerve fiber terminates is removed by more than the diameter of another muscle fiber from the blood vessel from which the nerve fiber deviated to

reach its termination. In some instances, a sympathetic fiber which apparently terminates on a striated muscle fiber also sends a branch into the wall of a blood vessel (Fig. 57, C).

In none of our preparations could we observe terminations of the fine unmyelinated nerve fibers on any considerable percentage of the muscle fibers. Obviously, it would be quite impossible to determine, by direct observation, whether sympathetic fibers terminate on all the muscle fibers or only on part of them. In most

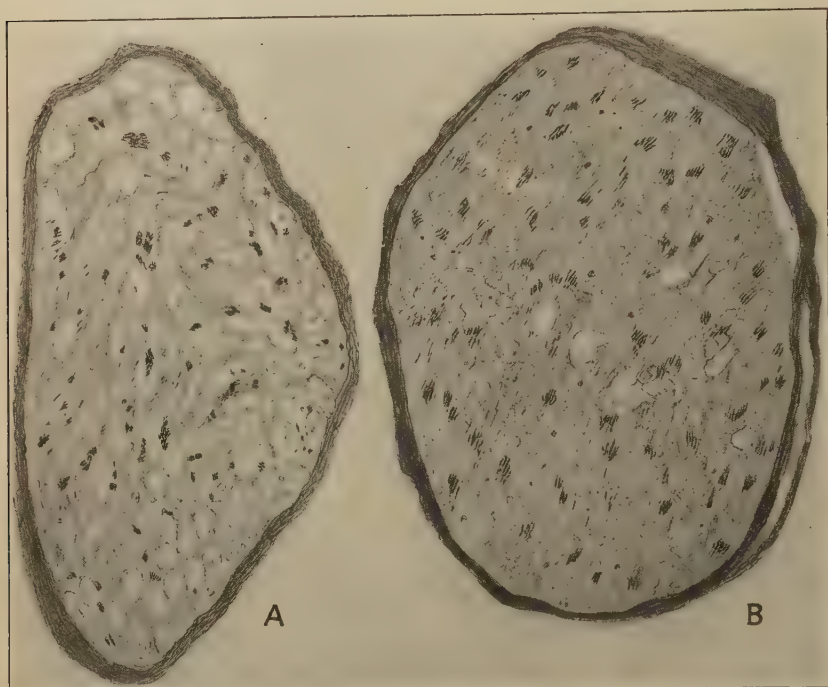
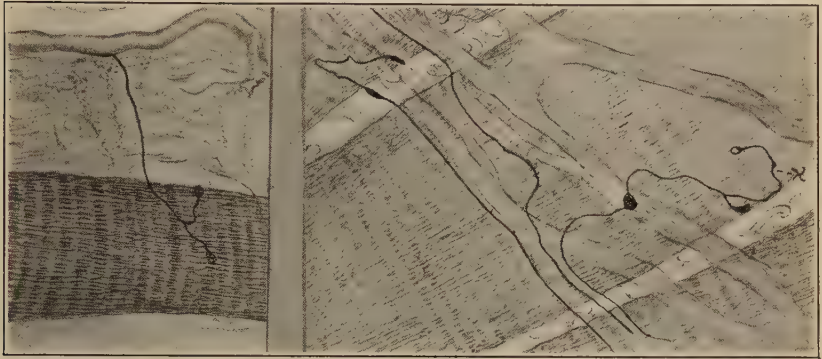


FIG. 56.—Camera lucida drawing of sections of nerves, illustrating the frequency and arrangement of unmyelinated fibers. *A*, Normal ramus to right triceps brachii muscle. *B*, Ramus to left triceps brachii muscle three weeks after section of the roots of the spinal nerves supplying the left fore limb, leaving the communicating rami intact (dog).

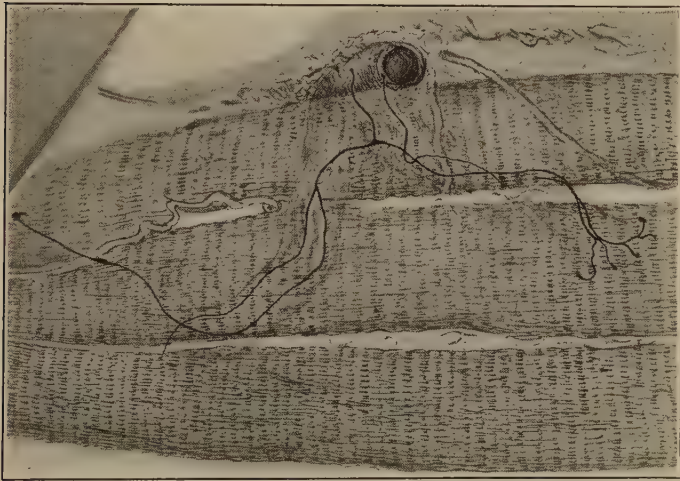
instances, only a short portion of a given muscle fiber can be observed in a single section. Furthermore, the location of the sympathetic termination, if present, may be unfavorable for observation. Neither can it be assumed that all the terminal structures are equally impregnated. Boeke found the "accessory" fibers most abundant in the eye muscles, where apparently the termination of an ordinary motor fiber and that of an autonomic fiber occurs on every muscle fiber. He found the accessory fibers somewhat less

abundant in the muscles of the tongue, and still less abundant in the muscles of the trunk and extremities. He did not, however, interpret the observed differences in the abundance of the fine un-



A

B



C

FIG. 57.—Camera lucida drawing, illustrating unmyelinated nerve fibers which terminate on muscle fibers in muscles of the extremities of the dog after degeneration of the spinal-nerve fibers. *A*, From a section of the quadratus plantæ muscle prepared four weeks after section of the spinal-nerve roots. *B*, From a section of a short flexor muscle of the foot prepared three weeks after section of the roots of the spinal nerves. *C*, From a section of a short flexor muscle of the foot prepared three weeks after section of the spinal-nerve roots (pyridine silver).

myelinated nerve fibers in his preparations as indicating corresponding differences in the abundance of the sympathetic supply to the respective muscles in question.

On the basis of his findings in the Ophidia, Kulschitsky (1924) advanced the opinion that certain of the striated muscle fibers, viz.: the thicker ones, receive only cerebrospinal nerve fibers, and others, viz.: the more slender fibers, receive only sympathetic fibers. Following this lead, Hunter and Latham (1925), on the basis of anatomical observations and the results of physiological experimentation, advanced the theory that, in birds and mammals, the white muscle fibers, *i. e.*, those containing a relatively small amount of sarcoplasm, receive only cerebrospinal nerve fibers, and the red muscle fibers, *i. e.*, those relatively rich in sarcoplasm, receive only sympathetic nerve fibers. Certain anatomical data bearing directly on this point cannot be reconciled with this theory. Boeke's

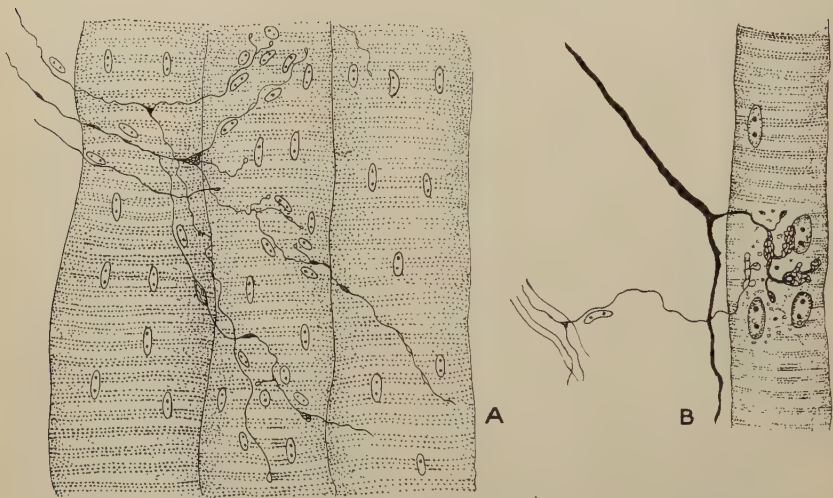


FIG. 58.—A, Sympathetic nerve-fiber terminating on skeletal muscle fibers. (Redrawn from Boeke and de Barenne.) B, Motor and plate and accessory-fiber termination on a skeletal muscle fiber. (Redrawn from Boeke: *Ztschr. f. mikr. Anat. Forsch.*, 1927, vol. 8.)

observations on the innervation of the eye muscles, cited above, indicate that probably every muscle fiber in these muscles is innervated by both a cerebrospinal and an autonomic fiber. In certain other striated muscles in which both white and red fibers are known to exist, particularly those of the mammalian tongue, Boeke found motor end-plates connected with ordinary myelinated nerve fibers on both the white and red muscle fibers. In some instances, he also found both an ordinary motor end-plate and a sympathetic termination on the same muscle fiber in other skeletal muscles. This finding was also corroborated in our preparations. Certain muscles which contain only red fibers, *e. g.*, the soleus of the rabbit (Hay, 1901), are also known to be innervated by cerebrospinal

fibers. In view of these facts, we cannot assume that any striated muscle fibers are innervated through the sympathetic system alone. On the other hand, the data available at present do not warrant the conclusion that all the striated muscle fibers receive both cerebrospinal and sympathetic nerve fibers.

Sympathetic Fiber Terminations.—The end structures through which the sympathetic nerve fibers terminate on striated muscle fibers consist mainly of delicate end-rings or end-loops and end-nets. In some instances, these terminal structures occur singly; in others two or more of them occur close together, each at the end of a terminal branch of the nerve fiber (Fig. 57). Terminations on adjacent muscle fibers are not infrequently connected with the same sympathetic fiber. In some instances, according to Boeke, the sympathetic fibers form a plexiform network with closed meshes between the muscle fibers, from which short branches arise to terminate on the muscle fibers. More complex terminal structures connected with fine unmyelinated fibers, presumably of sympathetic origin, have been described by various authors in skeletal muscles, particularly in lower vertebrates and young mammals.

The terminal structures on striated muscle fibers which are connected with the fine unmyelinated nerve fibers, as repeatedly described by Boeke, are hypolemmal in position and lie in intimate contact with the sarcoplasm. In some instances, they lie within the area of the motor end-plate or adjacent to it. In others, the position of the sympathetic fiber termination bears no apparent relation to that of the motor end-plate. Not infrequently, in pyridine-silver preparations, the area of the sarcoplasm in which the terminal structure lies is less heavily impregnated than the rest of the sarcoplasm and shows evidence of a very delicate granular sole plate.

Are Skeletal Muscles Supplied by Parasympathetic Fibers?—

The existence of a parasympathetic nerve supply to skeletal muscles has not been demonstrated beyond question by anatomical methods. That the cerebrospinal nerves contain many unmyelinated and small myelinated fibers which are not of sympathetic origin is well known. The majority of the unmyelinated fibers which remain intact in the spinal nerves following degeneration of the sympathetic fibers are components of the dorsal nerve roots (Hinsey, 1927). Many of these fibers are distributed through the muscular rami and probably terminate in the muscle. Boeke (1927) regarded them as components of the autonomic nervous system whose cell bodies lie within the central nervous system. This view is at variance with the accepted doctrine regarding the anatomical relationships of preganglionic and terminal neurons in autonomic efferent chains. Neither is the existence of unmyelinated afferent dorsal root fibers precluded by any anatomical data available at present.

That the muscles of the tongue (Imagawa, 1927) and face (Sakurasawa, 1927) and the extrinsic muscles of the eye (Sunaga, 1927) receive parasympathetic fibers has been maintained on the basis of histological changes observed in these muscles following parasympathectomy. That certain components of the dorsal nerve roots convey efferent impulses to the muscles of the extremities is strongly suggested, particularly by the work of Frank (1920). Kuré, Nitta *et al.* (1928) also advanced certain experimental anatomical data which seem to indicate the existence of efferent fibers in the dorsal roots of the lumbar nerves. They reported intact myelinated fibers of small caliber in the dorsal roots of the sixth and seventh lumbar nerves after the large myelinated fibers had undergone degeneration, following section of the dorsal nerve roots just proximal to the spinal ganglia. They regarded these as fibers which arise in the spinal cord and effect synaptic connections with special cells in the spinal ganglia. On the basis of these findings and the histological changes observed in muscles of the hind limbs following section of the dorsal roots of the lumbar nerves or removal of the spinal ganglia, they advanced the opinion that the muscles of the extremities also have a parasympathetic nerve supply. The data advanced by Kuré and his associates seem to be conclusive. Yet, in view of the negative results obtained in repeated attempts to demonstrate the existence of efferent fibers in the dorsal spinal nerve roots by anatomical methods, one would wish corroboration of these findings before accepting the existence of a parasympathetic nerve supply to the muscles of the extremities as an anatomical fact.

FUNCTIONAL SIGNIFICANCE OF THE SYMPATHETIC INNERVATION OF SKELETAL MUSCLES.

Sympathetic Innervation and Muscle Tonus.—General Experimental Data.—The earliest investigators who undertook to study the functional significance of the sympathetic innervation of skeletal muscles by the use of physiological and experimental methods, quite naturally surmised that whatever influence is exerted on skeletal muscles through the sympathetic nervous system must affect muscle tonus. As early as 1904, Mosso advanced the opinion that the unmyelinated fibers observed in skeletal muscles are sympathetic in origin and that they govern tonus and slow contraction. de Boer (1913), on the basis of experimental studies carried out mainly on frogs, advanced the theory that the tonus of skeletal muscles is mediated solely through the sympathetic nervous system. Although this theory obviously is erroneous, the experimental findings reported by de Boer focussed attention on muscle tonus as related to the sympathetic nervous system.

Lopez and von Brücke (1916) and de Barenne (1916) reported a

temporary diminution of tonus in the muscles of the hind limb on the side of the operation following unilateral extirpation of the lumbar sympathetic trunk in the cat. Salek and Weitbrecht (1920) reported that they could sometimes, but not invariably, demonstrate diminution of the tonus of the muscles of the hind limbs of frogs following deprivation of their sympathetic nerve supply. On the basis of experimental studies carried out on the frog, Maumary (1922) advanced the opinion that the tonus of skeletal muscles depends in part on their sympathetic innervation and in part on impulses emanating from the labyrinths.

Langelaa, in 1915, advanced the theory that muscle tonus consists of two distinct components, viz.: a "contractile" component concerned with movement and the assumption of posture, and a "plastic" component concerned with the maintenance of assumed posture, the former being mediated through the cerebrospinal, and the latter through the sympathetic nerves. On the basis of an extensive series of experiments carried out on frogs, he (1922) advanced the following conclusions: (1) Section of the seventh, eighth, and ninth communicating rami is followed by local shock of the primary reflex arcs of the spinal cord, during which the loss of tonus is complete, but as soon as the shock has subsided the loss of tonus is only partial. The muscles lose much of their plasticity. The effect of this is most apparent in the attitudes of the animal; the movements of the affected limb also lack steadiness. The results of diminished plasticity are gradually compensated by stimuli emanating from the labyrinths, especially from the one on the opposite side. (2) Section of the dorsal roots of the seventh, eighth, and ninth spinal nerves is followed by local shock of the primary reflex arcs of the spinal cord, during which the loss of tonus is complete. When the shock has subsided a diminution of tonus remains, but the postures and movements are approximately normal. The diminution of tonus seems to be due chiefly, though not exclusively, to a decrease in the contractile component. (3) Section of the spinal cord between the second and third spinal nerve roots is followed by shock in the posterior part of the body, during which the loss of muscle tonus is complete. When the shock has subsided, a diminution of tonus remains. Subsequent section of the communicating rami of the seventh, eighth, and ninth spinal nerves results in a diminution of the plasticity of the muscles of the hind limbs.

The observation of Langelaa, that the operative procedure involved in sympathetic denervation of the hind limb in the frog may result in local shock and consequent temporary atonicity of the limb muscles, probably explains de Boer's erroneous conclusion that sympathetic denervation of skeletal muscles results in complete loss of tonus. His finding that a diminution of tonus remains when the shock has passed off, the loss of which is gradually compensated,

is in accord with the findings of Lopez and von Brücke, de Barenne, Maumary, and others. His conception of contractile and plastic tonus as distinct components mediated through separate systems of nerve fibers, although not supported by the results of later investigations, played an important rôle in many of the subsequent discussions of muscle tonus as related to the sympathetic nervous system. In contrast to the observations cited above, many investigators, including Cobb (1918), Takahashi (1922), Newton (1924), Coman (1926), Tower (1926), and others, using various mammals as the experimental animals, were unable, by direct methods of observation, to detect even a temporary diminution in the tonus of the limb muscles following deprivation of their sympathetic nerve supply.

In our own experimental studies on cats and dogs (Kuntz and Kerper, 1926), we were unable, except possibly in a few cases, following sympathetic denervation of a limb, to detect a diminution of tonus in the muscles of that limb by direct observation or palpation of the muscles while the animal was in the waking state. When the animal was subjected to surgical anesthesia, however, the muscles of the limb deprived of its sympathetic innervation became more flaccid than those of the other limbs. When the animal, under deep anesthesia, rested on its back in a symmetrical position, so that the force of gravity acted equally on the limbs on both sides and postural reflexes due to an asymmetrical position of the head and neck were obviated, the limb deprived of its sympathetic innervation almost invariably dropped to a lower position than the one on the opposite side. In the case of either the fore or hind limbs, the difference in the posture of the limb deprived of its sympathetic innervation and the one on the opposite side was sufficiently well marked, under these conditions, to be easily observed. We were able to demonstrate this phenomenon in all but a few animals in a relatively large series. Coates and Tiegs (1928) stated that they were unable, in a series of five dogs, to corroborate these findings.

On the basis of a series of experiments carried out on birds (fowls and sea gulls), Hunter (1924) reported that the adducted position characteristic of the wing at rest is no longer fully maintained following section of the sympathetic trunk immediately caudal to the roots of the nerves which make up the brachial plexus. Since the preganglionic efferent neurons whose axons enter the cervical sympathetic trunk are components of the upper thoracic nerves, Hunter interpreted this result as indicating that the plastic tonus of the wing muscles is mediated through their sympathetic innervation. Following section of the dorsal roots of the lower four cervical nerves, he found that the wing exhibited a tendency to remain in any position in which it was passively placed. This tendency was less apparent when the dorsal root of the first thoracic nerve was also

cut. Hunter regarded the observed tendency of the wing to remain in whatever position it was passively placed, following section of the dorsal cervical nerve roots, as due to the plastic component of tonus mediated through the sympathetic nerves, and assumed that this tendency became less apparent following section of the dorsal root of the first thoracic nerve by reason of the fact that this nerve root contains many of the afferent fibers supplied to the wing through the sympathetic trunk. Following section of the sympathetic trunk just below the brachial plexus, and the dorsal roots of the lower four cervical nerves, he found that the wing tended to hang dependent. This he regarded as due mainly to the loss of plastic tonus. Hunter interpreted these findings as proving conclusively that the plastic tonus of the wing muscles is subserved by their sympathetic innervation.

In a series of experiments carried out on fowls and pigeons (Kuntz and Kerper, 1925), we corroborated most of Hunter's observations cited above. We did not confirm his observation that section of the dorsal root of the first thoracic nerve alone results in drooping of the wing comparable to that which he observed following section of the sympathetic trunk just below the brachial plexus. We were at that time inclined to accept Hunter's interpretation of these findings. We have since discovered, however, that section of the sympathetic trunk just below the brachial plexus does not result in appreciable drooping of the wing if the operation is carried out with a minimum amount of traumatic injury to the nerves of the brachial plexus. Coates and Tiegs (1928) also reported that section of the sympathetic trunk below the brachial plexus, in their experiments, did not result in appreciable drooping of the wing when the proper operative precautions were observed. The loss of the influence of the sympathetic innervation in the posture of the bird's wing, as in that of the mammalian limb, is readily compensated, in the normal behavior of the animal, by the cerebrospinal nerves.

We have also observed, since the results of our earlier experiments were reported, that section of the dorsal roots of the nerves of the brachial plexus, if carried out without injury to the spinal cord, does not result in appreciable drooping of the wing in all cases. Hunter's observation that the deafferented wing tends to remain in any position in which it is passively placed can, however, be fully corroborated. That the deafferented wing, when drawn down, is not immediately replaced to its normal position by the bird was already observed by Trendelenburg (1906). Coates and Tiegs (1928) also recorded similar observations. We do not now regard the tendency of the wing to remain in whatever position it is passively placed, following section of the dorsal roots of the nerves of the brachial plexus, as due to a component of tonus which is

mediated through the sympathetic nerves, but rather as the result of the loss of the sense of position of the wing due to interruption of the proprioceptive fibers in the dorsal nerve roots. The muscles of the deafferented wing are not atonic. If the wing is drawn down to the fully dependent position and somewhat away from the bird's body; it does not remain in that position when released, but recoils to the bird's side. It is also subject to voluntary control, and may at any time be replaced voluntarily into its normal position. In view of these facts, it may be stated that the recorded data bearing on the effect of nerve section on the posture of the bird's wing afford no unmistakable evidence of the existence of a sympathetic component in the normal tonus of the wing muscles. Neither do they disprove the existence of such a component.

Ducceschi (1922) reported marked diminution of the postural tonus of the external ear in rabbits, following extirpation of the superior cervical sympathetic ganglion. His findings were criticized by Hotto (1925). In a more recent paper, Ducceschi (1925) confirmed his earlier findings and pointed out clearly that a difference in the posture of the two external ears, following unilateral extirpation of the superior cervical sympathetic ganglion, usually cannot be observed unless the animal is at rest or feeding in an undisturbed condition. He also observed that the external auditory meatus has a somewhat greater diameter on the side of the operation than on the opposite side while the animal is at rest.

Experiments Involving Decerebrate Rigidity.—The characteristic posture of the limbs of mammals in a state of decerebrate rigidity is well known. It has been assumed by some that if muscle tonus is mediated solely or in part through the sympathetic nervous system, sympathetic denervation of a limb would either prevent the onset of decerebrate rigidity in that limb or bring about a diminution in the degree of rigidity exhibited by the extensor muscles.

De Barenne (1916) reported a lesser degree of extensor tonus, during decerebrate rigidity, in the limb deprived of its sympathetic innervation in some, but not in all cases. Van Rynberk (1917) and Cobb (1918) failed to observe any effect of sympathetic extirpation on decerebrate rigidity. Royle (1924) reported diminished extensor tonus during decerebrate rigidity, in the affected limb, following unilateral lumbar sympathectomy, as a fairly constant result in his experiments on goats. He emphasized the advisability of performing sympathectomy sometime before the decerebration experiment is carried out, in order to avoid any sensory disturbances which might result from the wound caused by sympathectomy. He also employed intratracheal anesthesia before decerebration and aerated the lungs with fresh air afterward. "In all these experiments," he stated, "the onset of decerebrate rigidity was characterized by extension of all four limbs, but the left lower limb could

be much more easily relaxed than the right. In the intervals, when the rigidity of the lower limbs was less, it was seen that the characteristics of decerebrate rigidity, as described by Sherrington (1896), were not present. If the right lower limb, for example, were passively extended, the limb tended to remain in extension; if the left one were extended, the limb would fall into a flexed position as soon as it was released."

More recently, Kanavel, Pollock, and Davis (1924), Meek and Crawford (1925), Huggett and Mellanby (1925), Ranson and Hinsey (1926), Coman (1926), Tower (1926), and Forbes *et al.* (1926) reported the results of decerebration experiments in which they could detect no significant effect of sympathetic denervation of a limb on the extensor tonus in that limb during decerebrate rigidity. On the contrary, Coombs and Tulgan (1925) reported that, in their decerebration experiments following extirpation of both stellate ganglia, "the rigidity of the fore limbs was very much diminished while the rigidity of the hind limbs persisted unchanged."

In the majority of the decerebration experiments reported, except those of Royle, cats and dogs were used as the experimental animals. In order to repeat Royle's experiments as nearly as possible, Mortensen, Friedbacher, and Quade (1928) carried out decerebration experiments in a series of goats, following unilateral lumbar sympathectomy. Like the majority of the recent investigators who used other mammals, they were unable to demonstrate any constant effect of sympathectomy on the extensor tonus in the corresponding limb during decerebrate rigidity. Occasionally, they observed differences in the extensor tonus of the two hind limbs while the animal was in a certain position, but found that by changing the position the difference in tonus would disappear. Since the postural reflexes remain unaltered by decerebration, precautions must be taken to avoid such reflexes, particularly those due to changes in the position of the head and neck, while comparing extensor rigidity on the two sides. Possibly, the diminished extensor tonus observed in certain cases, during decerebrate rigidity, in a limb deprived of its sympathetic innervation, could be explained on the basis of postural reflexes due to an asymmetrical position of the animal.

The results of the decerebration experiments cited above show clearly that the exaggerated extensor tonus of decerebrate rigidity is not mediated through the sympathetic nervous system, but they do not disprove the theory that the sympathetic nerves play a rôle in the maintenance of normal muscle tonus. Neither do they afford any positive evidence of real value bearing on the functional significance of the sympathetic innervation of skeletal muscles. As is well known, decerebrate rigidity follows destruction or impairment of the rubrospinal system. The exaggerated extensor tonus characteristic of this condition depends mainly on efferent impulses

which reach the extensor muscles via the somatic efferent fibers. The component of tonus mediated through these fibers is greatly exaggerated. Unless the influence of the sympathetic fibers on muscle tonus were equally exaggerated (which is not the case), the absence of the sympathetic influence on the tonus of the muscles of a limb deprived of its sympathetic innervation might easily escape detection during decerebrate rigidity, except by very accurate quantitative methods. In view of the central nervous mechanisms involved, and the important rôle of the somatic efferent fibers in the exaggerated extensor tonus in the extremities of decerebrate preparations, it must be apparent that experiments involving decerebrate rigidity are not well adapted to reveal the influence of the sympathetic innervation on the tonus of skeletal muscles.

Tonus Measurements.—Although muscle tonus has been the subject of many investigations, few investigators have employed quantitative methods in the study of this problem. Spiegel (1923) described a method for the study of tonus in the extensor muscles of the knee in which the results of actual measurements of the resistance of the resting muscles to passive extension are expressed in the form of a tonus curve. He showed, by the use of this method, that the tonus curve of the normally innervated quadriceps femoris, both in man and other mammals, rises very slowly at the beginning of passive extension, and then more rapidly as the length of the muscle is increased. Evidently a mechanism exists which tends to hold the muscle in its normal resting posture (brake phenomenon of Rieger). Spiegel also showed that this mechanism is still effective in animals following section of the tendons of the flexor muscles of the knee, *i. e.*, the tonus curve of the extensor muscles obtained following section of its antagonists is identical with that obtained while the antagonists are intact. He also showed that the brake phenomenon persists following elimination of the voluntary innervation by light anesthesia, and that it disappears following degeneration of the dorsal funiculi in the spinal cord in tabetic patients. He regarded this as the result of interruption of the proprioceptive reflex arcs. The brake phenomenon, according to Spiegel, depends on sustained reflex stimulation which tends to hold the muscle at whatever length is imposed on it by reflex contractions. The efferent neurons involved in this reflex mechanism are independent of the pyramidal system, since the brake phenomenon persists and may even become exaggerated following pyramidal lesions. It is usually not demonstrable in cases of flaccid paralysis, although the rapid components of the tendon reflex mechanisms may still be intact. This dissociation of the tendon reflex and the brake phenomenon, according to Spiegel, shows clearly that the central mechanisms of the static and kinetic innervation of the extensor muscles are in a large measure independent of each other.

Spiegel's method may also be used for measuring the resistance of the triceps brachii and extensor muscles of the manus in animals to passive extension. In a series of recent papers (Kuntz and Kerper, 1924, 1926), the results of several series of experiments were presented in which the difference in the tonus curves of the quadriceps femoris and triceps brachii in cats and dogs, obtained by the use of Spiegel's method, before and after sympathetic denervation, was taken as the criterion of the influence of the sympathetic innervation of an extensor muscle on its tonus. In the majority of these experiments, the measurements were carried out while the animal was under light ether anesthesia. As was pointed out by Spiegel and verified by us, light ether anesthesia does not appreciably affect these measurements, but in order still further to insure the validity of the measurements, they were, in many of our later experiments, carried out in mid-brain animals, *i. e.*, animals in which the brain stem was transected at the caudal level of the thalamus. This operation, if successfully carried out, does not affect the normal distribution of muscle tonus (Magnus, 1916). Neither does it result in any diminution of tonus while the muscle is in a resting condition. In our experiments, tonus measurements carried out on an extensor muscle in the same animal both before and after section of the brain stem at this level, but under otherwise similar conditions, were essentially identical. As soon as the animal emerges from anesthesia, following section of the brain stem, and the initial shock of the operation has subsided, postural reflexes may be elicited and the animal may assume a normal posture. As pointed out by Magnus (1924), it may even exhibit pseudo-affective responses to adequate stimuli. Animals in this condition, since they require no anesthesia and exhibit no voluntary movements, lend themselves advantageously to experiments involving tonus measurements carried out according to this method.

Spiegel's method as employed by us may be described briefly as follows. The apparatus (Fig. 59) consists essentially of a narrow leg board (*LB*) to the upper end of which is attached a transverse bar (*CB*), two lever rods (*LR*) attached to the ends of the transverse bar and bent at an angle of 135 degrees with the leg board and a hinged support (*F*) which is clamped to a vertical rod (*VR*) extending downward from the board on which the animal rests. The hinged support consists of a curved fork (*F*) and two rods (*R*) which are attached to the under surface of the leg board. These rods extend approximately 3 cm. from the upper end of the leg board and are bent so that the axis of rotation of the hinge (*H*) falls approximately 0.5 cm. below the plane of the under surface of the leg board. A protractor, from the center of which a weighted silk thread is suspended, is attached, with its plane edge parallel with the plane of the leg board, to one end of the transverse bar. A light scale pan is suspended from the distal ends of the lever rods. The board which carries the apparatus is clamped to a table.

For carrying out the measurements on the quadriceps femoris muscle, the

animal is placed on the board so that the pelvis projects beyond its free end just far enough to permit the hind limbs to hang with the thighs in the vertical position. The limb in question must hang between the rods extending from the upper end of the leg board. The leg is fixed to the under surface of the leg board, the upper end of which is concave to avoid pressure on the flexor tendons, so that the axis of rotation of the knee coincides with the axis of rotation of the hinge. The apparatus is then adjusted so that the femur is in a vertical position and the quadriceps femoris does not press against the end of the board on which the animal rests.

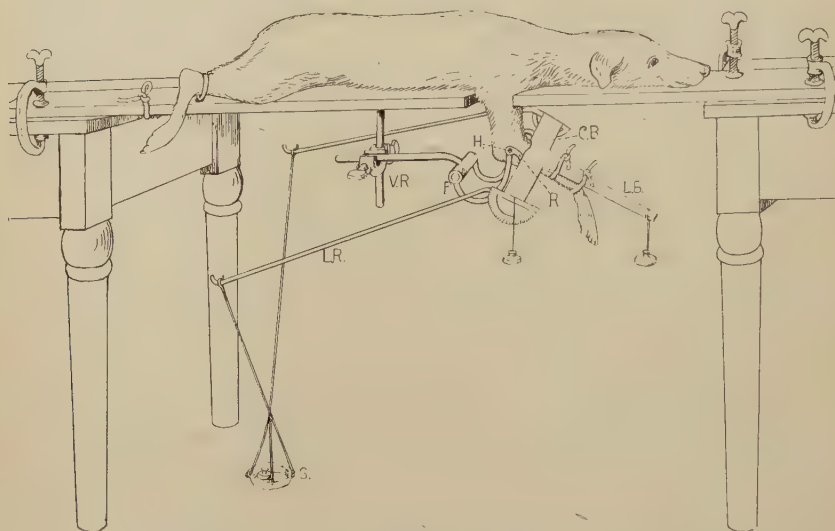


FIG. 59.—Apparatus for measuring resistance of extensor muscles to passive extension. (For explanation, see text.)

When the measurements are to be carried out on the triceps brachii muscle the animal is placed in the reverse position on the board which carries the apparatus. The free end of another board which is clamped to a second table of the same height as the first is brought into juxtaposition with the free end of the board which carries the apparatus. The neck and head of the animal rest on the second board; its fore limbs hang between the opposed ends of the two boards on which the animal now rests. The limb in question hangs between the rods which project from the upper end of the leg board. The antebrachium is now fixed to the under side of the leg board, so that the axis of rotation of the humero-radial articulation coincides with the axis of rotation of the hinge. The manus is left free. Fixation of the manus to the leg board was found to vitiate the results of the experiment by reason of the increasing tension of the flexors of the manus as the angle of the antebrachium with the vertical increases. Animal and apparatus are now adjusted so that the brachium rests in a vertical position and the triceps does not press against the end of the board which carries the apparatus.

When the measurements are to be carried out on the extensor muscles of the manus, the animal is placed on the two boards in such a position that the brachii rest horizontally on the board which carries the apparatus

and the antebrachii hang vertically between the juxtaposed ends of the two boards, the limb in question hanging between the rods which extend from the upper end of the leg board. The manus is now fixed to the under surface of the leg board so that the axis of rotation of the radiocarpal articulation coincides with the axis of rotation of the hinge.

In order to obtain a complete tonus curve, the muscle in question must be near its minimum normal length at the beginning of measurement. If the angle between the leg board and the vertical is large, indicating a relatively large degree of flexion of the limb, this angle may be reduced to 20 degrees or less by loading the lower end of the leg board. The apparatus with the animal's limb in position constitutes a balanced system. Any weight added to the scale pan will bring about some rotation of the hinge and corresponding flexion of the limb, by which passive extension of the muscle in question is brought about. The degree of rotation is read off on the protractor.

Whenever the apparatus is balanced, the sum of the forces applied on one side of the axis of rotation, tending to rotate in one direction, is equal to the sum of the forces applied on the opposite side, tending to rotate in the opposite direction. This equality, in the case of the dead animal, is expressed by equation:

$$I \quad x' l_1 \cos \alpha + Q_1 q_1 \cos \alpha = (U u + G l_2 + Q_2 q_2) \cos \beta$$

In this equation x' is the weight in the scale pan; Q_1 , the weight of the lever rods; Q_2 , the weight of the leg board; U , the weight of the leg and foot; G , the weight attached to the leg board to bring about the desired degree of extension of the knee; l_1 , l_2 , q_1 , q_2 , u , respectively, the distances from the axis of rotation at which the respective weights are applied; α and β , the angles respectively of the lever rods and the leg board with the horizontal. In the case of the living animal equation I becomes equation

$$II \quad x'' l_1 \cos \alpha + Q_1 q_1 \cos \alpha = (U u + G l_2 + Q_2 q_2) \cos \beta + T t$$

In this equation T is the tension of the extensor muscle; t , the distance of the tendon from the axis of rotation of the joint; x'' , the weight in the scale pan. Equation II minus Equation I is expressed as follows:

$$T t = (x'' - x') l_1 \cos \alpha$$

α is not measured and y is the angle of the leg board with the vertical.

$$\alpha + \beta + 135^\circ = 180^\circ, \text{ and } \beta = 90^\circ - y$$

Therefore,

$$T = (x'' - x') \cos (y - 45^\circ) \frac{l_1}{t}$$

In this equation y is the angle read off on the protractor; x'' , the weight in the scale pan; x' , the weight in the scale pan necessary for the same value of y in the case of the dead animal; l , the length of the lever rods; t , the distance of the extensor tendon from the axis of rotation of the joint for the corresponding position of the leg. The tonus curve is plotted by using the values of T , as calculated for the successive positions of the leg, as the abscissæ and the angles of flexion as the ordinates.

If, at the beginning of measurement, the limb, when adjusted in the apparatus, is in full extension or but slightly flexed, the extensor muscle in question will be at or near its minimum normal length at

the beginning of passive extension. The normal tonus curve, *i. e.*, the curve of passive extension of an extensor muscle with normal innervation, obtained under these conditions, rises very slowly at the beginning, and then more rapidly as the degree of extension of the muscle is increased by passive flexion of the limb. It continues to rise rapidly until further passive flexion of the limb encounters increasing resistance due to the natural elasticity of the tissues on the flexor surface, when it again rises more slowly. Normal tonus curves of the quadriceps femoris, triceps brachii, and the extensor muscles of the manus are illustrated in Fig. 60. These curves conform very closely to the normal tonus curves of the quadriceps femoris published by Spiegel.

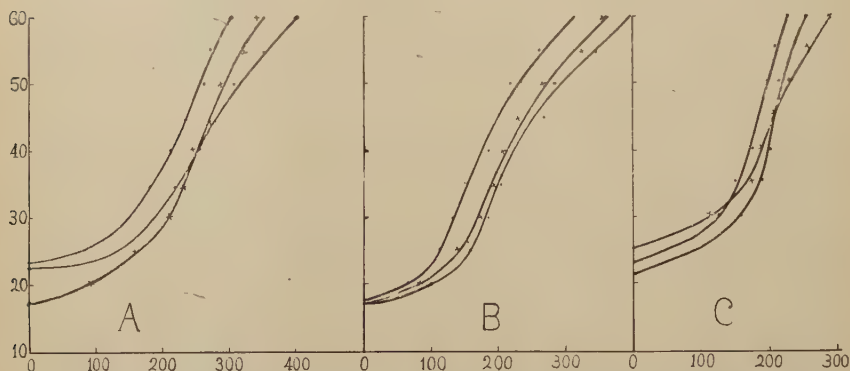


FIG. 60.—Normal tonus curves of the (A) quadriceps femoris, (B) triceps brachii, and (C) extensor muscles of the manus in cats and dogs. The figures in the vertical series represent the angle of flexion of the limb; those in the horizontal series represent the comparative values of the measurable tonus.

Elimination of the sympathetic innervation of the quadriceps femoris, by extirpation of the lumbar sympathetic trunk, in our experiments, almost invariably resulted in diminution of the resistance offered by this muscle to passive extension, in the absence of voluntary contraction. As indicated by the normal tonus curves (Fig. 60, A), this muscle, under normal innervation, offers considerable resistance at the beginning of passive extension, but the resistance gradually decreases as the degree of passive extension increases, *i. e.*, the brake phenomenon is exhibited in a well-marked degree. Following elimination of its sympathetic innervation, the tonus of this muscle, as manifested by its measurable resistance to passive extension, is materially diminished (Fig. 61, A, L and L'). Curves R and L, Fig. 61, A, are the tonus curves of the right and left quadriceps respectively obtained, following extirpation of the left lumbar sympathetic trunk, while the animal (cat) was under light ether anesthesia. Curves R' and L' are the corresponding tonus

curves obtained from the same animal three hours after section of the brain stem at the caudal level of the thalamus. While the corresponding curves taken before and after section of the brain stem do not coincide perfectly, they are nearly equal and show clearly that the results of the experiments are not vitiated by carrying out the measurements while the animal is under light ether anesthesia.

Experiments involving measurement of the resistance of extensor muscles of the fore limbs to passive extension before and after sympathetic extirpation were carried out on a large series of animals (cats and dogs). Sometimes the measurements were taken on the same side before and after extirpation of the stellate ganglion on that side. Sometimes they were taken on the same muscle of both fore limbs following unilateral sympathetic denervation. The tonus curves of both muscles were then compared. In a goodly number of experiments, the measurements were carried out in mid-brain animals. All these animals had been subjected to unilateral extirpation of the stellate ganglion before section of the brain stem was carried out. In some instances the measurements were first carried out while the animal was under light ether anesthesia and again several hours after section of the brain stem. In the majority of these experiments, the corresponding tonus curves derived from the measurements obtained before and after section of the brain stem are essentially similar and almost coincident.

The tonus curves of both the triceps brachii and the extensor muscles of the manus derived from measurements carried out before elimination of the sympathetic innervation of these muscles (Fig. 61, *B* and *C*), like those of the normal quadriceps femoris, rise very slowly at the beginning and then more rapidly as the length of the muscle is increased by passive extension until flexion of the limb reaches a relatively high degree. The tonus curves derived from measurements carried out on these muscles following elimination of their sympathetic innervation (Fig. 61, *B* and *C*), like the corresponding curves of the quadriceps femoris, rise more rapidly from the beginning. These curves indicate that the triceps brachii and extensor muscles of the manus, like the quadriceps femoris, exhibit diminution of tonus, while at rest, following elimination of their sympathetic innervation.

In the results of the experiments set forth above, the influence of the sympathetic innervation on the tonus of a resting muscle is manifested only by diminution of the resistance offered by the muscle to passive extension. In order to obtain tonus curves which actually represent a component of tonus which is mediated through the sympathetic innervation and at the same time obviate any possible effect of changes in circulation due to interference with the innervation of the blood vessels supplying the limb, tonus measure-

ments were carried out on the triceps brachii muscle following section of both roots of the sixth, seventh, and eighth cervical nerves within the spinal canal. This operation completely eliminates the somatic innervation of the triceps, but, since the preganglionic neurons in the visceral efferent chains supplying the limb are components of thoracic nerves, it leaves the sympathetic innervation of the entire limb intact. Consequently, the efferent innervation of blood vessels is not interfered with by the operative procedure. Tonus curves based on measurements carried out on the triceps brachii following section of both roots of the sixth, seventh, and

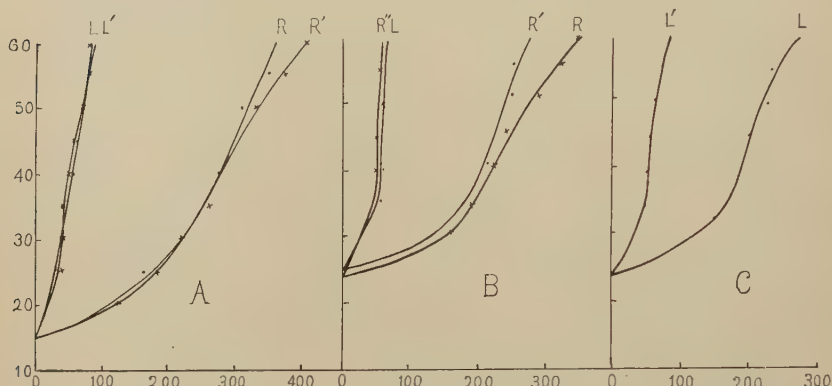


FIG. 61.—Tonus curves of extensor muscles with and without sympathetic innervation. (A) *R* and *L*, tonus curves of right and left quadriceps respectively of a cat following extirpation of left lumbar sympathetic trunk, animal under light ether anesthesia; *R'* and *L'*, tonus curves of right and left quadriceps respectively in the same animal three hours after section of the brain-stem at the caudal level of the thalamus. (B) *R* and *L*, tonus curves of right and left triceps respectively of a dog following extirpation of the left inferior cervical sympathetic ganglion. The measurements were carried out four hours after section of the brain-stem at the caudal level of the thalamus, before and after extirpation of the left inferior cervical sympathetic ganglion respectively. (C) Tonus curves of the left extensor muscles of the manus of a dog before (*L*) and after (*L'*) extirpation of the left inferior cervical sympathetic ganglion, animal under light ether anesthesia.

eighth cervical nerves, compared with the normal tonus curves of this muscle (Fig. 62), show a diminution of tonus, but, as indicated by the slow rise in the first part of the curve, the muscle still exhibits the brake phenomenon. This is well illustrated by curves *R'* and *L'*, Fig. 62, *B*, which are the tonus curves of the right and left triceps muscles respectively of the same animal (dog) following section of the roots of the sixth, seventh, and eighth cervical nerves on the right, and extirpation of the inferior cervical sympathetic ganglion on the left side. Since the entire spinal nerve supply to the triceps is derived from the sixth, seventh, and eighth cervical

nerves, section of the roots of the first thoracic nerve has no influence on the tonus measurements carried out on the triceps. The curves obtained following section of the roots of the first thoracic, in addition to those of the sixth, seventh, and eighth cervical nerves, are essentially identical with those obtained following section of the roots of only the cervical nerves.

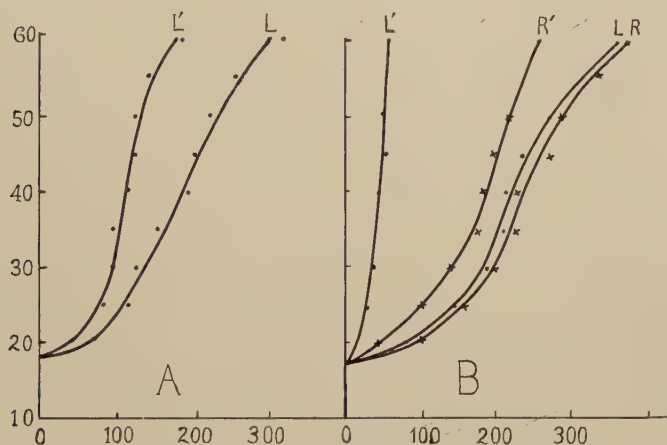


FIG. 62.—(A) Tonus curves of the left triceps of a cat before (*L*) and after (*L'*) section of both roots of the sixth, seventh, and eighth cervical nerves, leaving the sympathetic innervation of the fore limb intact. (B) *R* and *L*, normal tonus curves of the right and left triceps respectively of a dog. *R'*, tonus curve of the right triceps following section of both roots of the sixth, seventh, and eighth cervical nerves on the right side. *L'*, tonus curve of the left triceps following extirpation of the left inferior cervical sympathetic ganglion.

Following section of the roots of the nerves which supply the cerebrospinal innervation of the fore limb, leaving its sympathetic innervation intact, the muscles undergo atrophy and the extensors gradually lose the component of tonus which was still measurable immediately after section of the spinal nerve roots. In two dogs in our series in which the roots of only the sixth, seventh, and eighth cervical nerves were cut, measurements carried out on the triceps brachii three weeks after spinal root section still revealed a measurable component of tonus. On the other hand, measurements carried out on the triceps in three other dogs three weeks after section of both roots of the fifth, sixth, seventh, and eighth cervical and first thoracic nerves, leaving the sympathetic innervation of the limb intact, failed to reveal any measurable tonus.

In criticizing the results of our earlier experiments, Fulton (1926) raised the following objections: (1) "Experimental analysis of tonic reactions in the intact animals, in which various extraneous reflex factors cannot be excluded, are unreliable." (2) "The 'active'

muscle not being isolated by complete denervation of the surrounding muscular and cutaneous structures, especially of the antagonistic muscles, renders difficult and uncertain the interpretation of their responses." (3) Possibly the differences in the resistance of the muscle to passive extension are due to secondary circulatory changes. (4) The brake phenomenon "can be little other than a manifestation of the stretch reflex, since it was elicited by extension of an antigravity muscle." He suggested that the diminution in the resistance of the muscle to passive extension indicated by the difference in the curves obtained before and after sympathectomy may be due to modified responses of the proprioceptive endings in the muscle brought about by alterations in the blood supply.

The difficulties attending the analysis of tonic reactions in the intact animal are fully recognized. We do not regard the results of our experiments as affording the data necessary for an analysis of tonic reactions, but only as indicating that the sympathetic nerves exert an influence in the normal tonus of skeletal muscles in the absence of active contraction. An influence of the intact flexor muscles is not precluded, but the fact that Spiegel obtained tonus curves of the quadriceps femoris, following section of the tendons of its antagonists, which are essentially identical with the curves obtained while the flexor tendons were intact, strongly suggests that curves obtained, under the conditions of our experiments, are not materially modified by reason of the intact antagonists. Neither is an influence of circulatory changes due to sympathetic denervation precluded in the results of our experiments. There are, however, no data available at present which clearly indicate that the changes in circulation following sympathectomy exert either a direct or an indirect effect on muscle tonus. Furthermore, the majority of the recorded observations bearing on the effect of sympathectomy on the blood supply of the affected parts in animals indicate that the blood supply returns approximately to the preoperative level in ten days to two weeks after operation. In many of our experiments, the tonus measurements were carried out more than two weeks after sympathectomy.

The effect of sympathetic denervation on the so-called brake phenomenon was overemphasized in our earlier reports. We do not regard this phenomenon as dependent on the sympathetic innervation alone, although the curves obtained, following sympathectomy, in many of our experiments, rise almost as rapidly at the beginning as throughout the later part of their course. Many of the curves obtained following sympathectomy show clearly that the brake phenomenon still persists. Obviously, any appreciable diminution of the resistance of the muscle to passive extension must also affect the brake phenomenon, as manifested in the curves obtained by the method employed in these experiments.

Coates and Tiegs (1928) claim to have repeated our experiments on dogs deprived of the left lumbar sympathetic trunk, but were unable to confirm our findings. Their brief report does not include a description of the apparatus nor the procedure followed. Neither is it evident that their experiments are entirely comparable to ours, since the curve which they derived from measurements carried out on the normally innervated limb does not conform closely to the curves derived from measurements carried out on normally innervated hind limbs in our experiments. It may be stated in this connection that, in the case of a few animals in our series, the curve derived from measurements carried out after sympathectomy was almost identical with the curve obtained before sympathectomy, but in the great majority of cases the difference was unmistakable.

The experimental data set forth above show quite clearly that the resistance of an extensor muscle to passive extension is diminished following deprivation of its sympathetic nerve supply, and that an extensor muscle deprived of its spinal nerve supply, but with its sympathetic innervation intact, still offers greater resistance to passive extension than the completely denervated muscle, until the muscle has undergone some degree of atrophy. Nevertheless, the loss of the influence of the sympathetic innervation of a limb on the tonus of its muscles, at least in the animals studied by us, is so completely compensated by the cerebrospinal nervous mechanisms, under normal physiological conditions, that the deficiency cannot usually be detected by palpation of the muscles or by direct observation. Delicate quantitative methods are, therefore, of primary importance in detecting the influence of the sympathetic innervation in the tonus of skeletal muscles. Furthermore, since the influence of the voluntary innervation is constantly changing during muscular activity, quantitative methods designed to reveal the influence of the sympathetic nervous system in skeletal muscle tonus can be successfully applied only while the muscle is at rest, *i. e.*, while it does not exhibit active contraction.

While the results of our experiments are not expressed in definite units of measurement, they are quantitative. The method used is also sufficiently delicate to reveal changes in tonus which are quantitatively minute. That which is actually measured is the resistance offered by the muscle to passive extension. It may be objected that this is not tonus. The tonic state of the muscle must, however, be regarded as an important factor in determining the resistance offered to passive extension. Since, under the condition of the experiments, the curve of resistance of the atonic muscle is regarded as a vertical line, the curve of resistance of the muscle under complete or partial innervation may properly be regarded as the tonus curve.

Since sympathetic denervation of the muscles of a limb cannot

be accomplished without impairment of vasomotor control, the measurements carried out on the triceps brachii, following section of the roots of the spinal nerves through which this muscle is supplied, leaving the sympathetic innervation of the fore limb intact, assume primary importance by reason of the fact that the vasomotor innervation of the fore limb remains unimpaired as well as by reason of the fact that the tonus curve obtained represents a positive component of tonus which is subserved through the sympathetic innervation alone.

The tonus exhibited by an extensor muscle, in the absence of active contraction, as manifested by the resistance offered by the muscle to passive extension, is quantitatively small. Furthermore, any deficiency in tonus due to the loss of the sympathetic innervation is quite completely compensated, in the normal postures and activities of the animal, by the cerebrospinal innervation. It is not surprising, therefore, that so many investigators failed, in the absence of quantitative methods, to detect any diminution of tonus in the affected muscles following sympathectomy.

The mechanism by which the influence of the sympathetic innervation in muscle tonus is exerted is not known. Nor is there any advantage in postulating a sympathetic component of tonus which differs in quality from the tonus which is mediated through the cerebrospinal nerves. The conception of contractile and plastic tonus may be useful, but the theory that plastic tonus is subserved by the sympathetic nerves alone is untenable.

The results of tonus measurements carried out on the quadriceps femoris in four patients who underwent bilateral lumbar sympathetic ganglionectomy were reported recently in a preliminary paper (Kuntz, 1927). These measurements were carried out according to the method described by Spiegel (1923) for measuring the resistance of the quadriceps femoris to passive extension in man. The results obtained by this method are expressed in tonus curves which are comparable to the tonus curves derived from measurements carried out in animals according to the method described above. Two of the patients, men afflicted with thrombo-angiitis obliterans, were available for study both before and after operation. The other two were available for study only after operation. One of these, a young woman, had undergone the operation one year previously for the relief of Raynaud's disease; the other, a man afflicted with thrombo-angiitis obliterans, underwent the operation six days before the measurements were carried out.

These patients exhibited no appreciable changes in muscle tonus referable to the disease. The tonus curves obtained in the two patients before sympathectomy lie well within the range of normal variation. These curves, two of which are illustrated in Fig. 63, rise slowly until the angle of the leg with the extension of the thigh

approaches 30 degrees, after which they rise more rapidly. They are essentially normal tonus curves. The curves obtained after sympathetic ganglionectomy, in all the patients, rise more rapidly from the beginning. Those obtained from the patients who were available for study before operation also indicate appreciable diminution of tonus. In the absence of tonus curves based on measurements carried out before operation in the other two patients, the diminution of quadriceps tonus referable to sympathectomy, in these cases, cannot be estimated. The form of the curves obtained following sympathectomy suggests diminution of tonus.

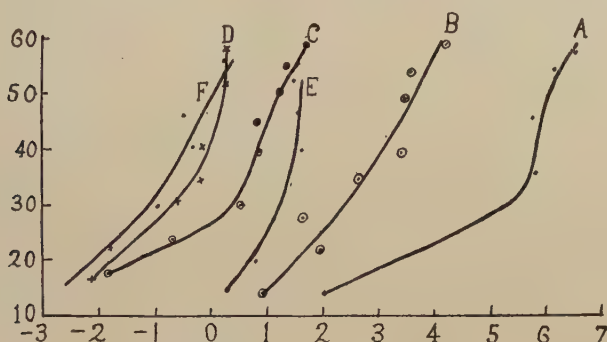


FIG. 63.—*A*, tonus curve of right quadriceps femoris obtained just before lumbar sympathectomy; *B*, tonus curve of the same muscle obtained just after lumbar sympathectomy; *C*, tonus curve of right quadriceps femoris obtained just before lumbar sympathectomy (another patient); *D*, tonus curve of the same muscle obtained just after lumbar sympathectomy; *E*, tonus curve of left quadriceps femoris (another patient) obtained six days after lumbar sympathectomy; *F*, tonus curve of left quadriceps femoris (another patient) obtained one year after lumbar sympathectomy.

Clinical Data.—Clinical data bearing on the rôle of the sympathetic nerves in the production and maintenance of muscle tonus are as yet meager. The beneficial effects of sympathetic ganglionectomy and ramisection in the treatment of spastic paralysis, as reported in certain cases, particularly by Royle (1924, 1927), Carrell (1926) and Von Lackum (1929) strongly suggests that the exaggerated tonus exhibited by the spastic muscles is due at least in part to impulses conveyed to the muscles through the sympathetic nerves. Kuré and his associates (1927) recently advanced certain clinical data which seem to indicate that sympathectomy results in diminution of the hypertonus in certain cases of spastic paralysis, particularly those in which the spasticity is the result of a pyramidal lesion. According to their observations, these cases commonly exhibit heightened sympathetic tonus and are benefited by sympathectomy, whereas, cases in which the spasticity is due to an extrapyramidal lesion frequently do not exhibit heightened sym-

pathetic tonus, and are not benefited by sympathectomy. In contrast to these findings, certain other surgeons, notably Kanavel, Pollock, and Davis (1925) observed no change in the tonus of spastic muscles following sympathectomy, although they applied this operation in a wide variety of cases.

On the basis of a clinical and experimental study of muscle tonus in man by the use of Mosso's apparatus, Flarer (1925) reported that the resistance of the gastrocnemius and soleus muscles to passive extension is increased by the administration of adrenalin, pilocarpin or atropin, but is diminished by the administration of novocain or histamin. He interpreted these results as indicating that the tonus exhibited by skeletal muscles, in the absence of active contraction, is mediated through their sympathetic innervation. Kuré and his associates (1922, 1925) also reported heightening of the tendon reflexes by the administration of adrenalin, particularly in cases in which these reflexes were already exaggerated before the adrenalin was administered. In certain cases they were able, by the administration of adrenalin, to convert a pseudo-clonus into an actual clonus with regular rhythm and relatively long duration. They also reported improvement of the muscle tonus, by the use of adrenalin, in tabetic patients with hypotonic muscles. They interpreted these results as supporting the theory that muscle tonus is maintained in part through the sympathetic system.

Sympathetic Innervation and Muscular Fatigue.—Certain experimental data advanced during the past few years seem to indicate quite clearly that the sympathetic innervation of skeletal muscles plays an important rôle in sustained muscular activity. Certain other data, on the contrary, do not support this theory.

Hunter (1925) reported that birds with one wing deprived of its sympathetic innervation showed the effect of this deficiency in increasing degree during prolonged flight. He also reported that a sea gull with both wings deprived of their sympathetic innervation was apparently exhausted after a few short flights. In contrast to these observations, Tower (1926) concluded, on the basis of her experiments on dogs, that "the capacity for prolonged muscular work and the onset and severity of fatigue were in no way affected by sympathectomy."

The results of a series of experiments designed to reveal the possible influence of the sympathetic innervation in sustained muscular contraction were reported by us in a preliminary paper (Kuntz and Kerper, 1924). In animals (dogs and cats) previously subjected to unilateral extirpation of the lumbar sympathetic trunk, a single muscle (gastrocnemius, tibialis anterior) was isolated, leaving its blood and nerve supply intact. The tendon was divided at its insertion and connected by a strong cord with an ergograph or a loaded muscle lever. The nerve supplying the muscle was then

stimulated by means of a tetanizing current which was kept constant throughout a given experiment. The apparatus was adjusted so that the muscle in question was under slight tension. Tetanic stimulation was applied and the curve of tetanic contraction of the muscle recorded. After an interval of rest the same procedure was carried out on the corresponding muscle on the opposite side. The curves of tetanic contraction of both muscles were then compared. Some of these experiments were carried out in animals under anesthesia, and others following section of the brain stem. The curves of tetanic contraction obtained while the animals were under anesthesia were highly inconstant. Those obtained following section of the brain stem were relatively more constant, but still showed variability in a marked degree. In some experiments, the contraction curve of the muscle deprived of its sympathetic innervation, in others that of the normally innervated muscle was obtained first. The order in which the curves were obtained seemed to have no important bearing on their form.

In order to obviate the possible effect of changes in the circulation through the muscle, due to interference with the innervation of the blood vessels on the side of the operation, and constriction of the blood vessels due to stimulation of the sympathetic fibers on the unoperated side, some of the experiments were made, under otherwise similar conditions, but with the common iliac arteries ligated. It is probably safe to assume that the volumes of blood flowing through the same muscle in both legs did not differ materially, by reason of the conditions of the experiment, while no blood was flowing through the common iliac arteries.

In the majority of these experiments, the initial contractions of both muscles were approximately equal in amplitude, but the tetanus curve of the muscle previously deprived of its sympathetic innervation dropped to the base line somewhat more rapidly than that of the normally innervated muscle. This seemed to indicate that a normally innervated muscle, when subjected to tetanic contraction, is able to resist fatigue somewhat longer, under otherwise constant conditions, than a muscle deprived of its sympathetic innervation. The results of our more recent experiments involving tetanic contraction, however, do not support this interpretation. In these experiments, the same muscle in both hind limbs of an animal previously subjected to unilateral extirpation of the lumbar sympathetic trunk was thrown into tetanus at the same time by means of the same electrical stimulation of the corresponding nerves. Simultaneous contraction curves were recorded by means of standardized ergographs. In order to avoid the variable effects of anesthesia, the experiments were carried out following section of the brain stem. In the majority of these experiments, both muscles exhibited equal resistance to fatigue. We must conclude, therefore, that the

results of our earlier experiments involving tetanic contraction of the muscles were not unequivocal. In the light of the results of the later experiments, the conclusion that the sympathetic innervation of skeletal muscles plays an important rôle in the capacity of these muscles to maintain tetanic contraction elicited by electrical stimulation is unwarranted.

In another series of experiments designed to reveal the influence of their sympathetic innervation on the capacity of skeletal muscles to resist fatigue, the results of which have not been published hitherto, the same muscle of both hind limbs, usually the tibialis anterior, in an animal (dog or cat) which had previously undergone unilateral extirpation of the lumbar sympathetic trunk, was made to contract against a load at uniform short intervals until it was no longer able to lift the load at each successive stimulation. In these, as in the experiments involving tetanic contraction, the muscle in question was isolated, leaving its blood and nerve supply intact. The tendon was divided at its insertion and connected by means of a strong cord to a loaded muscle lever. The same stimulus was used in the case of both muscles. Contractions were elicited at the same rate against equal loads. In some of the experiments, first one, and, after an interval of rest, the other muscle was thrown into activity until it failed to lift the load at each successive stimulation of the nerve. More commonly stimulation was applied on both sides simultaneously, *i. e.*, both the normally innervated muscle and the one deprived of its sympathetic innervation were made to contract simultaneously. To avoid the effects of anesthesia, these experiments were carried out following section of the brain stem. Sufficient time was allowed, following sympathectomy, to insure functional degeneration of the sympathetic fibers. In order to obviate the effect of a difference in the volume of the blood flowing through the two muscles, the experiment was carried out, in some instances, while the common iliac arteries were ligated.

The results of these experiments were fairly constant. When the contractions were elicited in each muscle separately, the time until the muscle failed to lift the load at each stimulation varied somewhat, but not uniformly in favor of the same muscle. The amplitude of the contractions of both muscles was approximately equal. When both muscles were made to contract simultaneously, they invariably resisted fatigue equally. Reduction of the blood supply by ligation of the common iliac arteries hastened the onset of fatigue equally on both sides. Under the conditions of these experiments, the sympathetic innervation of the muscles in question did not appreciably influence their contractile power or their capacity to resist fatigue.

In contrast to these results, Coates and Tiegs (1928) reported the results of similar experiments which seem to indicate a marked

effect of the sympathetic innervation on the resistance of an isolated muscle to fatigue. In animals (several goats and a dog) which had been subjected to extirpation of the left lumbar sympathetic trunk three to four months earlier, the gastrocnemius or tibialis anterior muscle on both sides was isolated, the branches of the sciatic nerves supplying other muscles were severed and the proximal ends of the sciatic nerves were crushed in order to abolish reflex control of the muscle, the tendons of both muscles were attached to levers which recorded on a slowly rotating drum the contractions produced by short tetanic shocks at the rate of 2 to 3 per second. Both nerves were stimulated simultaneously from the same induction coil. In some instances, the femoral arteries were ligated while the nerves were being stimulated. In all but one of their experiments the normally innervated muscle resisted fatigue longer than the muscle deprived of its sympathetic innervation. Usually the rapid fatigue of the muscle deprived of its sympathetic innervation, according to their account, was in marked contrast to the greater activity of the normally innervated one.

In view of the results of our own experiments of a similar character, all of which were carried out within a relatively short time after sympathectomy, it seems not improbable that the striking difference between the capacity to resist fatigue exhibited by the normally innervated muscle and the one deprived of its sympathetic innervation, in the experiments of Coates and Tiegs, may be due at least in part to dystrophic changes in the muscle deprived of its sympathetic innervation for so long a time. That skeletal muscles exhibit dystrophic changes following sympathetic denervation has been amply demonstrated (Kuré *et al.*, 1927; Kerper, 1928).

The results of experiments of a somewhat different nature were reported by Ginetzinsky (1922) and Orbeli (1924). In Ginetzinsky's experiments, the isolated gastrocnemius of the frog was stimulated through the ventral roots of the eighth and ninth spinal nerves by short tetani five seconds in duration, at intervals of fifty-five seconds, and isometric records were obtained. The plateau tension developed in each successive response diminished progressively under these circumstances, but, if the sympathetic trunk were stimulated at the level of the seventh sympathetic ganglion during the fifty-five-second intervals, the diminution in the plateau tension did not occur during the first five or six tetanic responses. The sympathetic stimulation resulted in augmentation of the plateau tension during the first few tetanic responses, but alone it produced no apparent effect. In another series of experiments, Ginetzinsky (1926) brought about fatigue of the gastrocnemius of the frog in an atmosphere of hydrogen by stimulation of the roots of the eighth and ninth spinal nerves. In most of these experiments (75 per cent), stimulation of the sympathetic

trunk following the onset of fatigue also resulted in increasing the strength of the contractions and the resistance of the muscle to fatigue. This result was interpreted as showing that the effect of sympathetic stimulation on muscular activity is not due solely to increased oxidation of the products of metabolism. It strongly suggests that sympathetic stimulation actually retards the onset of fatigue.

In Orbeli's experiments, according to Brücke's (1927) report, the isolated gastrocnemius of the frog was made to contract at repeated short intervals (30 to 300 per minute) by stimulation of the ventral roots of the seventh, eighth, and ninth nerves. When the onset of fatigue became apparent in the diminution of the amplitude of the successive contractions, the sympathetic trunk was stimulated for twenty to sixty seconds and after a latent period of ten to thirty seconds the amplitude of the successive contractions again increased, the maximum effect occurring some time after the sympathetic stimulation had ceased. That this result is not due to spread of the stimulating current is indicated by the long latent period and the continuation of the effect after the cessation of sympathetic stimulation. The effect of secondary circulatory changes is also precluded, since the circulation was cut off. These results also suggest that sympathetic stimulation tends to increase the resistance of skeletal muscles to fatigue.

In contrast to the results reported by Ginetzinsky and Orbeli, Wastl (1925) was unable to demonstrate any direct effect of sympathetic stimulation on the activity of a muscle, following the onset of fatigue, either in the frog or the cat. In her experiments on the frog, contractions of the gastrocnemius were induced by stimulation of the roots of the eighth and ninth nerves by means of single induction shocks at the rate of 20 to 50 per minute, or short faradic currents (three-quarters to one second) at the rate of 15 to 30 per minute. The sympathetic trunk was stimulated for various lengths of time and at almost every possible point in the fatigue curve, viz.: when the muscle contracted strongly, at the first appearance of the onset of fatigue, and during the various stages of fatigue, until the muscle was nearly exhausted. In some of her experiments the circulation was cut off before stimulation was begun. In no case did she observe any effect of sympathetic stimulation on the contraction of the muscle when the spread of the stimulating current was precluded.

In Wastl's experiments on the cat, the isolated tibialis anterior, in the anesthetized animal with intact circulation, was made to contract against a loaded muscle lever by stimulation of the ventral roots of the sixth or seventh lumbar nerves (or both roots combined) with break shocks at a rate of 100 to 220 per minute. At various periods following the onset of fatigue of the muscle, the sympathetic

trunk was stimulated by means of a faradic current. Care was taken to observe that the sympathetic stimulation was effective, as indicated by good erection of the hairs of the tail. In the majority of these experiments, no effect of sympathetic stimulation on the contractions of the muscle was observed. In certain experiments, the amplitude of the contraction was decreased by sympathetic stimulation and the previous amplitude was regained only slowly after sympathetic stimulation ceased. Wastl regarded this result as due to the vasoconstriction caused by the sympathetic stimulation. On the basis of these findings, she concluded that sympathetic stimulation "does not increase the height of contraction of mammalian muscle fatigued by rapid single contractions and it decreases the height if it causes marked vasoconstriction."

Nakanischi (1927) reported the results of experiments on the frog which he interpreted as indicating that the resistance of an isolated muscle to fatigue brought about by stimulation of its motor nerve supply alone is increased by simultaneous sympathetic stimulation. More recently (1928) he reported the results of another series of experiments in which he studied the effect of successive sympathetic stimulation on an active skeletal muscle. In these experiments, carried out on the frog, the sympathetic trunk was divided between the sixth and seventh ganglia. The gastrocnemius muscle was thrown into tetanus by stimulation of the eighth or eighth and ninth nerves proximal to the communicating rami. During the tetanic contraction of the muscle, the sympathetic trunk was stimulated between the seventh and eighth ganglia by means of a current of threshold value for the peripheral sympathetic fibers, or but slightly stronger. After a latent period, the effect of the sympathetic stimulation was manifested by a rise in the curve and stabilization of the tetanic contraction which continued for a short time after the sympathetic stimulation ceased. In some instances, when both the eighth and ninth spinal nerves were stimulated, stimulation of the sympathetic trunk resulted in inhibition of the tetanic contraction which also continued for a short time following the cessation of sympathetic stimulation. Since this effect of sympathetic stimulation was not observed when the tetanic contraction was elicited by stimulation of the eighth spinal nerve alone, Nakanischi concluded that the ninth communicating ramus in the frog probably contains inhibitory fibers.

Maibach (1928) recently reported the results of experiments which may be regarded as a repetition of those reported by Orbeli. They were, however, carried out with more refined technique and under more rigidly controlled conditions. Using bloodless preparations of the frog, the isolated gastrocnemius or gracilis muscle was made to contract at uniform short intervals by stimulation of the ventral roots of the eighth and ninth spinal nerves. The sympathetic

trunk was stimulated by means of a current just above the threshold of sympathetic stimulation at various intervals during the activity of the muscle. Like Orbeli, Maibach found that when the sympathetic trunk was stimulated following the onset of fatigue of the muscle, as indicated by the gradual diminution of the amplitude

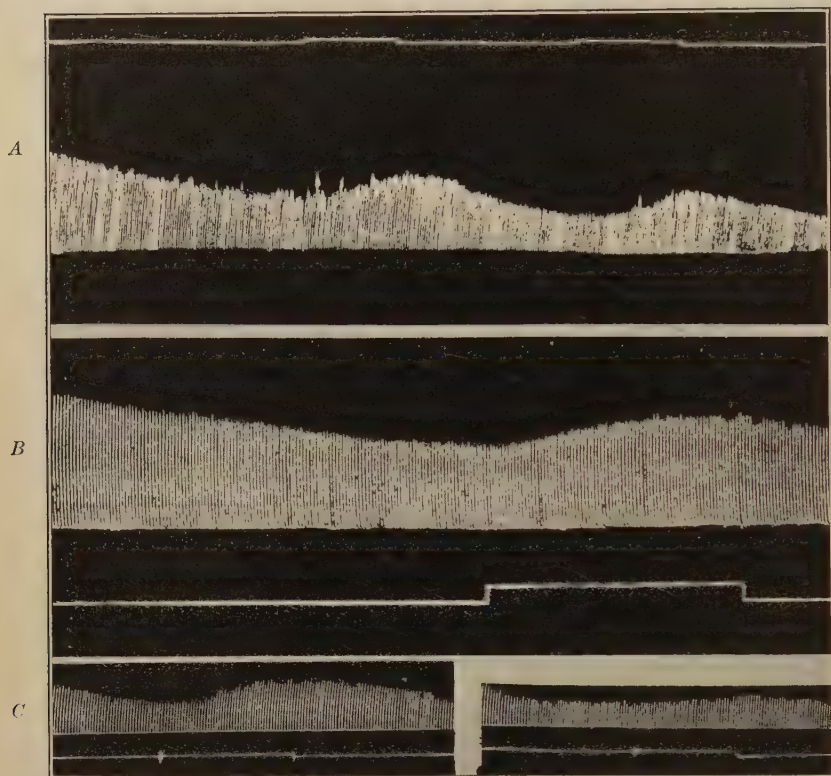


FIG. 64.—The effect of sympathetic stimulation on an active skeletal muscle of the frog. Successive contractions of the gastrocnemius or gracilis muscle were elicited by stimulation of the ventral roots of eighth and ninth spinal nerves. After the onset of fatigue, the sympathetic trunk was stimulated at intervals indicated by the time signal. It will be seen that the amplitude of the contractions gradually increased after a latent period. (A from Orbeli: *Pavlov Jubilee volume*, 1924; B and C from Maibach: *Ztschr. f. Biol.*, München, Germany, J. T. Lehmann's Press, 1928, No. 88, vol. 3.)

of the contractions, the amplitude of the contractions gradually increased after a latent period of several seconds, reached a maximum, and then gradually decreased. The effect of sympathetic stimulation always continued for a short time after stimulation of the sympathetic trunk ceased. The results obtained with the muscle in air, but kept moist by frequent applications of a physio-

logical salt solution, and with the muscle immersed in a bath designed to compensate as nearly as possible for the lack of circulation and respiration were comparable, although the muscle became fatigued more rapidly under the former than under the latter conditions. When the sympathetic trunk was stimulated before the onset of fatigue of the muscle, it had no effect on the amplitude of the contractions. Maibach concluded, therefore, that muscular contraction is augmented by sympathetic stimulation only after the muscle has become somewhat fatigued.

The results reported by Maibach fully corroborate those of Orbeli. Like Orbeli, he concluded that sympathetic stimulation during muscular activity increases the capacity of the muscle to resist fatigue. Since the preparations used were bloodless, and comparable results were obtained both with the muscle in air and in a bath designed to restore physiological conditions as nearly as possible, the increased capacity of the muscle to resist fatigue cannot be regarded as the result of changes brought about through the vasomotor mechanism in response to sympathetic stimulation, but must be regarded as the effect of impulses conveyed to the muscle cells through sympathetic fibers. Whether the increased capacity of the muscle to resist fatigue is due to increased metabolism, facilitation of the removal of metabolites, or a more direct effect of sympathetic stimulation cannot be stated at present. In view of the experimental technique employed and the results reported by Maibach, it seems highly probable that the reported failures to corroborate Orbeli's findings were due mainly to faulty technique.

The results of the experiments of Ginetzinsky, Orbeli, Nakanischi, and Maibach, cited above, seem to be in accord with the observed effect of adrenalin on fatigued muscle. Cannon and Nice (1913) observed an increase in the working power of the tibialis anticus in the cat following stimulation of the peripheral end of the splanchnic nerve. This result was regarded as due at least in part to the action of adrenalin on the muscle. In Gruber's (1924) experiments, injection of adrenalin increased the amplitude of contraction, lowered the threshold of stimulation, and shortened the latent period for both fatigued and unfatigued muscle. He suggested, therefore, that adrenalin may exert a direct "trophic" action on the muscle, presumably through facilitation of the removal of metabolites. In Maibach's experiments, the addition of adrenalin in appropriate amounts to the bath in which the muscle was immersed, following the onset of fatigue, produced an effect similar to that of sympathetic stimulation. Lapicque and Nattan-Larrier (1922) also demonstrated that adrenalin reduces the chronaxie of a fatigued muscle, probably by facilitation of the removal of acid metabolites. On the contrary, Wastl (1925) reported that injection of small amounts of adrenalin intravenously, causing a decrease

or but a brief moderate rise of blood pressure, had little effect on the muscle contractions following the onset of fatigue. Sometimes the amplitude of contraction was slightly increased. When larger amounts of adrenalin were injected, causing a marked rise in blood pressure, she sometimes observed a decrease in the amplitude of the contractions.

As stated above, the results of our own experiments involving the capacity of the same muscle of the two hind limbs, in animals (cats and dogs) previously subjected to unilateral extirpation of the lumbar sympathetic trunk, to accomplish work under artificial stimulation failed to reveal an unmistakable influence of the sympathetic innervation on the capacity of the muscle to resist fatigue. We do not, however, regard our findings as militating against the positive results reported by Ginetzinsky, Orbeli, Nakanischi, and Maibach, since, in their experiments, the augmenting effect of sympathetic stimulation was observed only when the stimulus was applied following the onset of muscular fatigue, whereas, our experiments did not involve direct sympathetic stimulation. Although certain investigators have failed to observe a direct effect of sympathetic stimulation on the capacity of skeletal muscles to resist fatigue, we do not regard such negative findings as affording an adequate reason to question the corroborative findings of the four investigators named above. These findings have an important bearing on the functional interpretation of the sympathetic innervation of skeletal muscles, since any mechanism through which the capacity of skeletal muscles to resist fatigue is augmented must be of fundamental importance to the organism.

Influence of the Sympathetic Nerves on the Peripheral Apparatus of the Motor Nerves.—In a series of experiments carried out by Orbeli, the gastrocnemius muscle of the frog was fatigued by means of single induction shocks applied alternately to the ventral roots of the eighth and ninth spinal nerves and the muscle itself. Under these conditions, as reported by Ganttt (1927), sympathetic stimulation resulted in a sharp increase in the contractions elicited by indirect stimulation, but had no effect on the contractions elicited by direct stimulation of the muscle. In another series of experiments reported from Orbeli's laboratory, the sartorius muscle of the frog was immersed in Ringer's solution which was replaced at a certain moment by a 0.25 per cent solution of chloral hydrate. The motor root of the nerve or the muscle itself was stimulated at one-minute intervals by means of a maximal induction current. Usually the replacement of Ringer's solution by the solution of chloral hydrate resulted in equal diminution of the contractions elicited both by direct and indirect stimulation; after fifteen minutes indirect stimulation was no longer effective, but direct stimulation still provoked slight contractions. When, in these experiments,

the sympathetic trunk was stimulated, the reactivity of the muscle to direct stimulation was increased in some cases, and quickly dropped to zero in others. The reactivity of the muscle to direct stimulation was not affected by sympathetic stimulation. Orbeli concluded, on the basis of these results, that the influence of the sympathetic nerves on skeletal muscles is exerted through the peripheral apparatus of the motor nerves.

In a series of experiments, the results of which have not been published hitherto, we (Kuntz and Kerper) obtained certain evidence which also seems to support the theory that the sympathetic nerves exert an influence on the terminal apparatus of the somatic motor nerves or affect the irritability of the muscle fibers in some other way. These experiments were designed to show the effect of sympathetic extirpation on the facility with which viscerosomatic reflexes are elicited by stimulation of the visceral organs or mesenteric nerves. Attention has been called anew to reflex responses of skeletal muscles elicited by visceral stimulation particularly by the work of Sherrington (1918), MacKenzie (1918), and Carlson and Luckhardt (1921). Such viscerosomatic reflex responses are facilitated by decapitation of the experimental animal. Reflex responses of the hind limbs elicited by stimulation of the splanchnic nerves or the more peripheral mesenteric nerves which radiate from the celiac and superior mesenteric ganglia, in the decapitated cat, were described in detail by Miller and Simpson (1924). In view of these findings, it may be assumed that if reflex responses of skeletal muscles are facilitated by sympathetic stimulation, viscerosomatic reflexes would be elicited more readily in the normally innervated limb than in the limb deprived of its sympathetic innervation.

To insure complete sympathetic denervation of one hind limb, the experimental animals (cats) were subjected to unilateral extirpation of the lumbar and upper sacral portions of the sympathetic trunk. The spinal cord was transected at the level of the foramen magnum. After the initial shock of the latter operation had subsided, the visceral organs or mesenteric nerves were stimulated either mechanically or by means of an electric current. In all the animals in which the experiment was successful, reflex responses to both mechanical stimulation of visceral organs (pressure on the spleen, duodenum, or pancreas, inflation of the stomach, etc.) and electrical stimulation of mesenteric nerves were observed in the hind limb on the side on which the sympathetic trunk was left intact, but rarely in the hind limb deprived of its sympathetic innervation. Viscerosomatic reflexes involving the muscles of the hind limb on the side of the sympathectomy could only be elicited by visceral stimulation which was much more powerful than that required to elicit fairly vigorous reflex responses in the normally innervated

limb. In some animals, no reflex muscular reactions in response to visceral stimulation were observed in the hind limb deprived of its sympathetic innervation, although the stimulation employed was sufficiently strong to elicit vigorous reflex responses in the normally innervated hind limb.

Inasmuch as contraction of skeletal muscles cannot be elicited by sympathetic stimulation alone, it must be assumed that the efferent impulses involved in viscerosomatic reflexes are mediated through somatic motor fibers. Under the conditions of our experiments, the visceromotor reflex arcs on the side of the sympathectomy were not impaired. That the peripheral sympathetic fibers on the side of the intact sympathetic trunk were activated by the visceral stimulation employed was also apparent by reason of the reactions of the blood vessels and the erector pili muscles. It seems not improbable, therefore, that the difference in the degree of reactivity of the muscles of the two hind limbs to visceral stimulation was brought about by deprivation of the one limb of its sympathetic innervation. Whether the sympathetic influence on the normally innervated muscle is exerted on the motor end-plates or affects the reactivity of the muscle fibers in some other manner cannot be determined on the basis of these experiments.

As reported by Gantt (1927), the results of certain experiments carried out by Orbeli on dogs also showed that the thresholds of stimulation of the skeletal muscles on the two sides differed following unilateral extirpation of the abdominal sympathetic trunk. The experimental procedure employed was not reported, but the results were regarded as supporting Orbeli's hypothesis that the sympathetic nerves contain regulatory fibers for both the motor and sensory end apparatus.

Influence of the Sympathetic Nerves on Spinal Reflex Arcs.—The results of certain experiments reported from Orbeli's laboratory also seem to indicate that the sympathetic nerves exert an influence on the spinal reflex arcs. In a series of frogs, the spinal cord was transected in the foramen magnum and the brain destroyed. The aorta was ligated and the sympathetic trunk on one side was divided at the level of the fifth or sixth spinal nerve. The communicating rami of the eighth, ninth, and tenth nerves on this side were left intact. All the communicating rami on the opposite side were severed. The experiment was carried out an hour later. The reflex irritability was tested at intervals of five minutes according to Türk's method, *i. e.*, both hind feet were dipped in a 1 per cent solution of sulphuric acid and then rinsed with water. The reaction time, *i. e.*, the interval between the dipping of the feet in the acid and their withdrawal, was determined by means of a metronome. After several trials of this kind, the sympathetic trunk which remained connected with the eighth, ninth, and tenth nerves through

the communicating rami was stimulated (four minutes after the last trial) either by means of an induction current or a chemical substance (0.1 per cent nicotin), with the following results: (1) Lengthening of the reaction time on both sides; (2) shortening of the reaction time on both sides; (3) shortening of the reaction time only on the stimulated side; (4) lengthening of the reaction time on the stimulated side; (5) lengthening of the reaction time on the opposite side. These results were corroborated in eviscerated spinal frogs and toads. In the toads, the spinal canal was also laid open and the spinal cord denuded of part of its covering. On the basis of these results, Orbeli concluded that the sympathetic fibers exert a direct influence on the central part of the spinal reflex arc, although the possibility of an influence on the peripheral receptors is not precluded.

As stated by Gantt, Orbeli summarized the results of all his studies on the functional significance of the sympathetic innervation of skeletal muscles as follows: "The sympathetic nervous system exerts a profound influence over the physico-chemical changes occurring in skeletal muscle, accompanied by a modification of the functional ability of that muscle. These changes influence, it seems, the conditions of the motor end-plate, calling forth transformations in the efficiency of the corresponding muscles. This forms a sort of regulatory mechanism for the expenditure of muscle strength, and governs the conduction of impulses by the motor nerves. From this point of view the sympathetic innervation of skeletal muscle is an adaptive innervation through which the functional ability of the muscle is determined."

Influence of the Sympathetic Nerves on Muscle Metabolism.—That the ratio of the creatinin to the creatin content of skeletal muscle is determined at least in part by influences exerted through the sympathetic nervous system has been maintained by not a few investigators. It is well known, however, that creatin metabolism is increased during muscular activity; consequently, creatin metabolism cannot be dependent on sympathetic influences alone. As was pointed out by Langley (1922), the data bearing on this point indicate that creatin metabolism is influenced to a far greater extent by the somatic than by the sympathetic nerves.

According to Büttner (1926), the glycogen content of muscles is increased following sympathetic denervation. This finding was confirmed by Hoffmann and Wertheimer (1927), who also pointed out clearly that glycogen metabolism in skeletal muscles is subject to nervous regulation. When animals (cats and dogs) were starved, in their experiments, following unilateral section of the sciatic nerve, the glycogen content of the denervated muscles diminished much less rapidly than that of the normally innervated muscles. When animals were starved before section of the sciatic nerve and then fed abundantly, the glycogen content of the denervated muscles

was not appreciably increased. Periarterial sympathectomy, in their experiments, had but little effect on the glycogen content of the muscles. The results of certain of Büttner's experiments also indicate that the lactic acid content of skeletal muscles is increased following sympathetic denervation.

The influence of the sympathetic nerves on the processes of oxidation and reduction in skeletal muscles is well illustrated by the effect of sympathectomy and sympathetic stimulation on the reaction of the muscles to vital dyes. When a vital dye, *e. g.*, methylene blue, is injected into the lymph hearts of a frog, the muscles of the extremities become lightly stained. Hoffmann and Magnus-Alsleben (1922) observed that if the nerves supplying one of the hind limbs were cut following the injection of methylene blue into the posterior lymph hearts, the muscles of that limb assumed a more intense color than those of the other hind limb. In a further investigation of this phenomenon, they found that neither section of the dorsal nerve roots nor paralysis of the motor components alone exerted any influence on the staining reaction of the muscles. When the communicating rami of the seventh, eighth, and ninth nerves were divided, however, leaving the dorsal and ventral nerve roots intact, the muscles of the hind limb on this side assumed a more intense color than when the entire nerve supply to the limb was cut. This seemed to prove that the observed difference in the staining reaction of the muscles of the two hind limbs was due to section of the sympathetic fibers. They were also able to demonstrate that the more intense staining reaction of the muscles deprived of their sympathetic innervation was not due to an excessive amount of the dye taken up by the muscle fibers, but to retardation of the processes of reduction. When the lightly stained muscles of the normally innervated limb were treated with oxidizing agents, they also became intensely blue.

On the basis of results obtained in experiments designed to demonstrate the effect of sympathetic stimulation on the reaction of the skeletal muscles to methylene blue, Stepanoff (1923) and Krestownikoff (1926), working in Orbeli's laboratory, reported that the oxidative processes in skeletal muscle are augmented by sympathetic stimulation. By the use of the mikrorespirometer, Orbeli was also able to demonstrate a relative increase in O_2 consumption in skeletal muscles during sympathetic stimulation. This relative increase in the oxidative processes was manifested mainly in the retardation of the continuous decrease in O_2 consumption during muscular excitation and in the fact that the oxygen intake remained constant during sympathetic stimulation and for some time after its cessation.

That sympathetic denervation is followed by temporary dilatation of the capillaries in skeletal muscles has been observed repeat-

edly. The duration of such capillary dilatation is not definitely known. The data available at present strongly suggest that, in experimental animals (cat, dog, rabbit), the circulation through a limb deprived of its sympathetic innervation approximates the preoperative level within ten days or two weeks after operation. The results of experiments with vital dyes, reported by Gabbe (1926), show clearly that increased permeability of the capillaries immediately following sympathetic denervation is a factor in determining the rate at which certain materials are taken up by the muscle fibers. When 1 cc. of a 1 per cent solution of water blue was injected into a frog's heart, following sympathetic denervation of one hind limb, the muscles of that limb took up more of the dye than those of the normally innervated hind limb. Microscopic examination of the muscles also showed that the quantity of the dye which passed through the capillary walls, as indicated by the relative abundance of the dye particles in the pericapillary zones, was proportional to the degree of capillary dilatation. Increased permeability of the capillaries in the muscle tissue, following sympathetic denervation, and its effect on the intake of materials by the muscle fibers was also demonstrated, in Gabbe's experiments, by the use of other chemical agents. For example, muscles of the frog deprived of their sympathetic innervation were found to contain 200 per cent more urea than the normally innervated muscles forty minutes after injection of a 20 per cent solution of urea into the abdominal vein. Gabbe also showed that this increase in the urea content was independent of the water content of the muscle. In another series of experiments, he showed that muscles of the frog deprived of their sympathetic innervation give up water more readily than the normally innervated muscles when the osmotic pressure of the blood is increased by injecting a salt solution, *e. g.*, sodium chloride. This observation was also corroborated by Hoffmann and Wertheimer (1927).

Although the above data show clearly that changes in the blood vessels, particularly the increased permeability of the capillaries, play an important rôle in the metabolic changes observed in skeletal muscles immediately after sympathetic denervation, it cannot be assumed that all the metabolic changes referable to sympathetic denervation are due to vascular changes. On the basis of the results of experiments involving ligation of the blood vessels and the injection of caffeine in doses sufficient to produce maximal vasocontraction and irreversible rigidity, Büttner (1926) concluded that the metabolic changes observed in skeletal muscles following sympathectomy are brought about, at least in part, by the direct effects of sympathetic denervation. In this connection it is not without interest to recall that Claude Bernard (1871) discussed the possibility of a sympathetic influence in muscle metabolism which is independent of vasomotor control.

Histological Changes in Skeletal Muscles Following Sympathetic Denervation.—Although many investigators have reported the results of experiments designed to reveal the functional significance of the sympathetic innervation of skeletal muscles, few have observed any appreciable atrophic changes in the muscles following sympathetic denervation. Weight determinations of corresponding muscles on both sides, following unilateral sympathectomy, were reported by a number of investigators, but these data revealed no unmistakable effect of sympathetic denervation on the muscle. Histological studies of skeletal muscles following sympathetic denervation have been reported in but few instances.

In a study of the muscles of the diaphragm of the dog following partial and complete denervation, Kuré and Shimbo (1922) observed that degeneration of the cerebrospinal fibers of the phrenic nerve resulted in a degree of atrophy of the muscle in the area of the diaphragm affected, due to inactivity, but degeneration of both the cerebrospinal and sympathetic fibers in the phrenic nerve resulted in complete degeneration of the denervated diaphragmatic musculature. They also reported atrophic changes in the portion of the diaphragmatic musculature affected, following extirpation of the abdominal sympathetic trunks in young animals. Kuré, Hatano *et al.* (1925) reported the results of an extensive series of experiments, involving histological examination of muscles of the limbs at various intervals following sympathetic denervation. When the muscles were examined within a relatively short time following sympathectomy, they usually found no significant changes in the muscle fibers nor any proliferation of the interstitial tissue. When the histological examination was carried out a long time (six to ten months or longer) after sympathetic denervation, marked changes were apparent in most cases. The majority of the muscle fibers were atrophic and reduced in diameter, some of them being very slender. Many of the remaining fibers were abnormally large. These were described as hypervoluminous. The changes observed were not uniform throughout the cross-section of the muscle, but in certain areas the majority of the fibers were abnormally large, while in other areas, the majority of the fibers were reduced in size and few large fibers were present among the smaller ones. In certain intervening areas, the muscle fibers remained apparently normal. The cross striations remained well preserved in all the muscle fibers. The number of nuclei associated with the muscle fibers was increased. This was more apparent in the areas in which abnormally large fibers predominated than in the areas in which the majority of the fibers were atrophic. The interstitial connective tissue was also increased, particularly in the areas in which most of the muscle fibers were reduced in diameter.

Imagawa (1927) reported the results of a series of experiments

on dogs in which he cut the sympathetic, parasympathetic, and cerebrospinal nerve fibers to the anterior portion of the tongue in various combinations. Section of the chorda tympani alone, *i. e.*, section of the parasympathetic supply, resulted in distinct atrophic changes in the muscle of the corresponding portion of the tongue after a relatively long time. Extirpation of the superior cervical sympathetic ganglion alone also resulted in some degree of atrophy of the tongue muscles after a long time. Section of the hypoglossal nerve, which conveys both motor and sympathetic fibers to the tongue, also resulted in atrophy of the tongue muscles affected, but the changes did not become well marked for a relatively long time. When both the hypoglossal nerve and the chorda tympani were divided, the tongue muscles affected became markedly atrophic in a relatively short time. On the basis of these results, Imagawa concluded that both the sympathetic and parasympathetic as well as the motor cerebrospinal fibers take part in the trophic innervation of the muscles, and that elimination of any one of these components alone does not result in a high degree of atrophy by reason of the compensatory action of the other components.

The results of experiments of a somewhat similar character, involving the extrinsic muscles of the eye, were reported by Sunaga (1927). Following extirpation of the ciliary ganglion in young dogs, he described changes in the extrinsic eye muscles similar to those described by Kuré, Hatano, *et al.*, in muscles of the limbs following sympathetic denervation for relatively long periods. Extirpation of the superior cervical sympathetic ganglion alone also resulted in similar, but less marked atrophic changes in the eye muscles. When the cerebrospinal fibers supplying the eye muscles were cut, leaving the ciliary ganglion and sympathetic fibers intact, the eye muscles underwent atrophic changes less rapidly than when the ciliary ganglion was also extirpated. Like Imagawa, Sunaga concluded that both cerebrospinal and autonomic fibers take part in the trophic innervation of skeletal muscles.

Sakurasawa (1928) also reported dystrophic changes in muscles of the face (*M. caninus* and *M. levator labii*) in the dog following deprivation of their sympathetic or parasympathetic innervation or both. The facial nerve, through which these muscles receive their motor innervation, also contains sympathetic fibers derived from the superior cervical sympathetic ganglion. Parasympathetic fibers from the sphenopalatine ganglion probably reach these muscles via branches of the maxillary nerve. According to the results reported by Sakurasawa, section of the nerve of the pterygoid canal alone, *i. e.*, section of the preganglionic fibers to the sphenopalatine ganglion, resulted in but slight atrophic changes in the muscles of the face, but extirpation of the sphenopalatine ganglion resulted in marked muscular dystrophy within a month

after the operation. Section of the nerve of the pterygoid canal and the maxillary nerve distal to the sphenopalatine ganglion resulted in dystrophic changes in the muscles in question earlier than extirpation of the sphenopalatine ganglion without section of the maxillary nerve. Likewise, extirpation of both the sphenopalatine and superior cervical ganglia resulted in more marked changes in the muscles of the face than extirpation of either of these ganglia alone. He concluded, on the basis of these findings, that elimination of the parasympathetic innervation of the muscles of the face results in dystrophic changes in these muscles, and that these changes are hastened and also become more marked if the muscles are also deprived of their sympathetic innervation. Following bilateral section of the facial nerve and unilateral section of the maxillary rami distal to the infraorbital foramen, he observed less marked changes in the facial muscles on the side on which maxillary rami were left intact than on the opposite side. He concluded, therefore, that the parasympathetic nerves exert an influence which tends to inhibit the atrophic changes in muscles following section of their motor nerve supply.

Atrophic changes comparable to those observed in the muscles of experimental animals, following sympathetic denervation were also reported by Kuré, Tsuji, and Hatano (1926) in the muscles of the face and neck in man, following cervical sympathectomy in the treatment of disease.

In all the accounts of the histological changes observed in skeletal muscles following deprivation of their sympathetic or parasympathetic innervation or both by Kuré and his associates, the similarity of these changes and the changes commonly observed in the affected muscles in clinical cases of progressive muscular dystrophy were emphasized. Kuré (1928) also pointed out that the dystrophic changes observed in experimental animals following extirpation of a portion of the sympathetic trunk, like those observed in clinical cases of progressive muscular dystrophy, are more marked in the muscles of the face, shoulder girdle, arms and thighs, than in the muscles of the forearms and legs and the small muscles of the hands and feet. He explained this difference on the assumption, based on anatomical and physiological data, that the muscles of the former group are more abundantly supplied by autonomic nerve fibers than those of the latter.

In an investigation now in progress in our laboratories, Kerper (1928) described histological changes in some of the muscles of the fore limb of the dog, particularly the triceps brachii, two to three months after extirpation of the stellate ganglion, which, in general, are similar to the changes described by Kuré and his associates in muscles of the dog, but less marked. He found many of the muscle fibers reduced in diameter as compared with the fibers of the norm-

ally innervated muscle. In general, the myofibrils were less compactly aggregated and less distinct in the atrophic than in the normal fibers. The cross striations remained distinct, but the sarcomeres were longer in the affected fibers than in the fibers of the corresponding muscle on the unoperated side, although both muscles were removed and fixed under conditions as nearly as possible identical. The elongation of the sarcomeres, as determined by actual measurements carried out with the aid of the camera lucida, not infrequently approximated 20 to 25 per cent. Hyper-voluminous muscle fibers were less common in Kerper's material than in the material described by the Japanese investigators. Hyperplasia of the interstitial tissue was also less marked. Kerper's material was taken sooner, however, following sympathetic denervation, than that described by Kuré and his associates. Furthermore, as Kuré also pointed out, experimental animals exhibit a relatively wide range of variation in the rate at which the observable atrophic changes take place in the muscles following sympathetic denervation.

Conclusion.—In view of all the data bearing on the functional significance of the autonomic innervation of skeletal muscles, it must be apparent that the nervous influences exerted on the muscles through the autonomic nerves are not expressed in a single phase of the vital activity of the muscle fibers, but affect all the vital processes of the muscle cells. Much of the autonomic nervous influence on skeletal muscles is expressed through its effect on muscle metabolism, which must be regarded as being brought about in part through vasomotor control, including the nervous regulation of the permeability of the vascular endothelium, and in part through the direct effect of autonomic impulses on the muscle cells.

Most of the experimental data bearing on the relation of muscle tonus to the autonomic nervous system are inconclusive. In view of all the data available, however, it cannot be denied that muscle tonus is influenced directly or indirectly through the sympathetic nerves. The hypothesis that a definite plastic component of muscle tonus is dependent on a direct effect of the autonomic nerves on the muscle fibers is untenable.

That the reactivity of skeletal muscles to stimulation of the motor nerves is influenced by the sympathetic nerves seems to be demonstrated. Whether this influence is exerted through the motor end-plates or involves changes in the colloidal state of the protoplasm of the muscle fibers brought about by impulses mediated through the autonomic nerves remains to be determined.

Much of the experimental evidence bearing on the influence of the autonomic nerves on the functional capacity of skeletal muscles and their resistance to fatigue must also be regarded as inconclusive. That sympathetic stimulation increases the functional capacity and

retards the onset of fatigue of skeletal muscles through its direct influence on the muscle fibers cannot be regarded as demonstrated beyond question. In view of the important rôle of the autonomic nerves in muscle metabolism and the reactivity of the muscles to motor stimulation, it may be assumed that these nerves also play an important rôle in the functional capacity of the muscles. That lesions of the autonomic nerves may result in muscular weakness is evidenced by the atrophic changes observed following sympathetic and parasympathetic denervation.

CHAPTER XVI.

PATHOLOGY OF THE AUTONOMIC NERVOUS SYSTEM.

INTEREST in the autonomic nervous system in relation to disease has increased materially during the past two decades, but our knowledge regarding the histopathological changes in the autonomic ganglia and nerves and the significance of these changes has not been advanced in a corresponding degree. The majority of the studies carried out during this period which have a bearing on the rôle of the autonomic nervous system in disease deal mainly with the clinical and pharmacological aspects of the problem. Although a wide variety of pathological changes in the autonomic ganglia and ganglion cells have been described, the data bearing on the specific relationships of these changes to disease are as yet meager. These data were obtained mainly from preparations of material taken at autopsy following death due to a wide variety of causes. In most cases, it was quite impossible to establish a direct relationship between a specific lesion of the autonomic nervous system and a disease process by reason of the variety of pathological conditions represented in the cases in question, which not infrequently included some degree of senile degeneration. Nevertheless, the data available at present strongly suggest a direct relationship of the observed lesions of the autonomic system and the disease process in many acute and chronic clinical conditions. More exact knowledge regarding the nature and causes of lesions of the autonomic nervous system and the part they play in disease awaits further clinical and experimental investigation.

HISTOPATHOLOGY OF THE AUTONOMIC GANGLIA AND GANGLION CELLS.

The Chromidial Substance and the Nucleus-plasma Ratio.—The majority of the investigators who reported the results of histopathological studies of autonomic ganglion cells described changes in the abundance, distribution, and structure of the chromidial substance in both the nucleus and cytoplasm. In many instances, they also attempted to correlate the observed changes in the autonomic ganglion cells with a specific disease process, but in relatively few instances did they attempt to interpret the observed changes in these cells in terms of modified function.

That functional activity and depression of nerve cells result in changes in the quantity and distribution of their chromidial content is well known. In an extensive series of studies of the cytological changes brought about in nerve cells by physiological stimulation and depression, under experimental conditions, Dolley (1909-1918) found that changes in the quantity and distribution of the chromidial substance and variation in the nucleus-plasma ratio are natural consequences of functional activity and depression of these cells, and conform to the well-recognized biological principles expressed in Goldschmidt's (1904) theory of the functional significance of the chromidial apparatus and Hertwig's (1903) theory of the nucleus-plasma ratio. Hertwig's theory is essentially the expression of a constant mass relationship, but it carries with it an underlying reciprocal principle, viz.: the mutual interdependence and interchange of materials. In the nerve cells, as in many other cells, this interchange of materials involves the production and consumption of chromidial substance. Both nucleus and cytoplasm take part in its elaboration, and it is concerned mainly with function in the cell. During cellular activity, chromidial substance disappears not only from the cytoplasm, but also from the nucleus. The cell may become practically dechromatinized. Yet, after due rest, it regains its full complement of chromidial substance.

The orderly sequence of change involving the chromidial substance and the nucleus-plasma ratio in the Purkinje cells in experimental animals subjected to continued stimulation was described by Dolley (1911) as follows: The cell, which in the resting condition contains a variable amount of extranuclear chromidial substance and little intranuclear chromatin except in the nucleolus, first responds by increased chromatin production and becomes progressively hyperchromatic until the initial enlargement of the whole cell reaches its maximum. Following the stage of hyperchromatism, the cell begins to shrink and the hyperchromatism recedes until the chromidial content of the cytoplasm has become reduced to the average normal level, but the nucleus shows evidence of edema; consequently, the nucleus-plasma ratio is shifted in favor of the nucleus. The chromidial content of the cytoplasm suffers still further diminution until the secondary restoration of the cytoplasmic chromidial substance sets in. The chromidial substance is first piled up about the nuclear membrane and then displaced toward the periphery. Following this stage, secondary diminution of the chromidial substance sets in and continues until no chromatic material remains apparent except in the nucleolus. Finally this also passes out and the cell appears pale and exhausted. During the final stages of exhaustive activity, the nucleus-plasma ratio is shifted in favor of the plasma. In view of this succession of changes in the cell, it may be assumed that the chromidial substance in the cytoplasm,

derived through the nucleus, is used up during cellular activity and continually replaced by the mediation of the nucleus. At first the supply exceeds the demand, giving rise to hyperchromatism, but with long-continued activity the supply no longer equals the demand and the chromidial substance undergoes a progressive diminution until finally none remains in the cell.

Functional depression of a nerve cell may intervene during any phase of functional activity. The immediate result of functional depression, according to Dolley (1913), is cessation of extranuclear chromatin production. The extranuclear chromidial substance is gradually consumed, but the intranuclear chromatin cannot pass out; consequently, there is a relative or absolute increase of intranuclear chromatin associated with a deficiency of cytoplasmic chromidial substance, and the nucleus-plasma ratio is shifted in favor of the nucleus. If long-continued depression becomes a degenerative condition, shrinkage and dissolution of the nucleus take place and the cell may become reduced to a shrunken, anucleated, homogeneous, and hyaline mass.

The results of Dolley's anatomical analysis of the effects of stimulation and depression on nerve cells are in full accord with the recognized physiological classification of stimuli in three groups, viz.: pure excitants, pure depressants, and those which first excite and later depress. While there is a separate anatomical basis for fatigue of excitation and fatigue of depression, the manifestations of these two forms of fatigue must, in the main, be identical. In exhaustive activity, the production of chromidial substance fails; in depression, it is inhibited. Although nerve cells do not possess the capacity for rejuvenescence, they have the capacity for recovery within relatively wide limits. The process of recovery, whether from the effects of stimulation, depression, or disuse atrophy, involves the restoration of the same preëxisting materials, and, unless pigmentation has intervened, the cell may resume its normal cytological appearance.

Dolley's studies cited above involve mainly the Purkinje cells in the cerebellar cortex. Comparable studies of the effects of stimulation and depression on autonomic nerve cells have not been carried out. Isolated descriptions of the cytological appearance of autonomic ganglion cells in preparations of material obtained at autopsy in a wide variety of pathological conditions strongly suggest that the chromidial substance and the nucleus-plasma ratio undergo changes in the autonomic ganglion cells, under conditions of stimulation and depression, which conform very closely to the changes described by Dolley in the Purkinje cells. In an investigation based on material obtained at autopsy in a variety of pathological conditions, now in progress in these laboratories, Ingersoll has been able to recognize variations in the quantity and distribution of the

chromidial substance and in the nucleus-plasma ratio in autonomic ganglion cells which can be arranged in series which conform very closely to the series of changes described by Dolley in the Purkinje cells during excitation and depression. Some of these variations are illustrated in Figs. 65 and 66. The results of a limited number of animal experiments carried out in these laboratories also suggest that continued stimulation induces changes in the autonomic ganglion cells comparable to those described in the Purkinje cells, due to continued excitation.

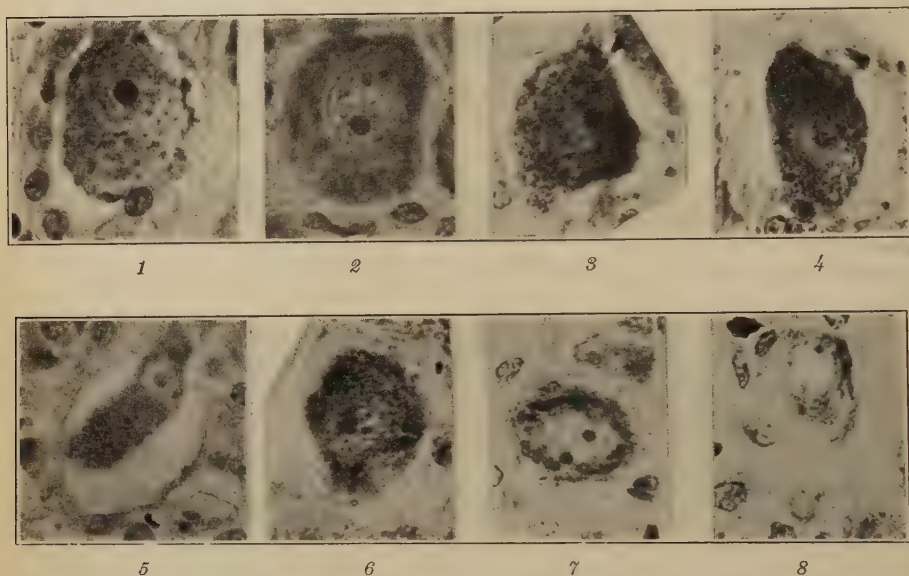


FIG. 65.—Autonomic ganglion cells (human), illustrating the progressive changes in the quantity and distribution of the chromidial substance and the nucleus-plasma ratio due to cellular activity. 1, resting cell; 2, early hyperchromatism; 3, advanced hyperchromatism; 4, early shrinkage of the cell and receding hyperchromatism; 5, advanced shrinkage of the cell and further recession of hyperchromatism; 6, reduction of cytoplasmic chromidial substance to normal level, with edema of both nucleus and cytoplasm, resulting in rounding out of the cell; 7, further reduction of the cytoplasmic chromidial substance; 8, almost complete depletion of the cytoplasmic chromidial substance and extrusion of the nuclear chromatin into the cytoplasm.

Certain pathological conditions result in more profound changes in the chromidial content of the autonomic ganglion cells than others. This probably is due to their stronger stimulating or depressing effect. For example, in arsenic poisoning and poliomyelitis, the chromidial bodies in the autonomic ganglion cells break up and the chromidial substance apparently goes into solution. In many cases, the chromatolysis involves the majority of the autonomic ganglion cells and terminates, in some instances, in

complete disintegration of many of these cells. The changes observed in the autonomic ganglion cells in cases of arsenic poisoning, in general, correspond to the changes which have been described in the neurons in the central nervous system in similar cases. In addition to chromatolysis they involve homogeneous swelling of the protoplasm and displacement of the nucleus toward the periphery. The occurrence of chromatolysis in the autonomic ganglion cells in cases of poliomyelitis shows clearly that this disease involves the autonomic ganglia as well as the gray substance in the spinal cord.

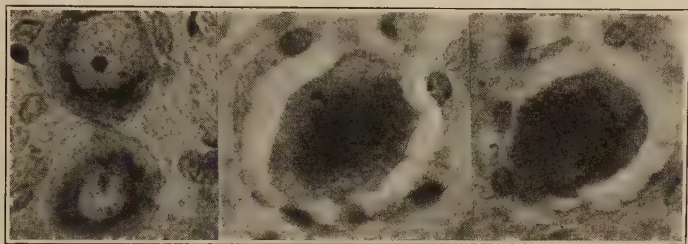


FIG. 66.—Autonomic ganglion cells (human), illustrating successive stages in functional depression.

During senility and cachectic states, the study of the changes in the chromidial substance is rendered more difficult by reason of the presence of pigment in the ganglion cells. In general, it may be stated that heavily pigmented ganglion cells contain relatively small amounts of chromidial substance. Careful study of the ganglion cells which are only moderately pigmented, in cases of senility or other conditions in which the majority of the autonomic neurons are laden with pigment, not infrequently reveals evidence of chromatolysis. The larger chromidial bodies in the peripheral zone of the cytoplasm become fragmented while the chromidial substance in the perinuclear zone appears in the form of minute particles (chromidial dust) or is actually in solution, leaving a perinuclear zone which is apparently free from chromidial substance. Fragmentation of the chromidial bodies and chromatolysis may continue until all the chromidial substance in the cell seems to be in solution. In Nissl preparations, such ganglion cells exhibit a homogeneous blue color with possibly a few heterogeneous patches (Vas, 1892; Laignel-Lavastine, 1906; Spiegel and Adolf, 1922). In cases of death due to burns, many of the autonomic ganglion cells exhibit fragmentation of the chromidial bodies, clumping of the chromidial substance, especially in the peripheral zone, and chromatolysis (Spiegel and Adolf, 1922).

Rapid disintegration of the chromidial bodies in the autonomic

ganglion cells has also been observed in many cases of acute infection. Some degree of chromatolysis, in many cases almost complete dissolution of the chromidial substance, was reported by Mogilnizcky (1923) in cases of pneumonia, septicemia, diphtheria, and tetanus. He also observed varying degrees of disintegration of the chromidial bodies in the autonomic ganglion cells in cases of miliary tuberculosis.

Pigmentation.—The occurrence of pigment in the autonomic ganglion cells in man is not only a striking phenomenon, but is of peculiar interest in relation to intracellular metabolism. Although pigment is observed only rarely in the autonomic ganglion cells of animals (cat, dog, rabbit), except under experimental conditions, a moderate degree of pigmentation of these cells is a common phenomenon in man after middle age, and not infrequently occurs even in the young. While moderate pigmentation of the autonomic ganglion cells in man after middle age and even earlier does not necessarily indicate morbidity, exaggerated pigmentation of these cells probably is always pathological. Certain pathological conditions, *e. g.*, arsenic poisoning, cachexia, and senile atrophy are always accompanied by exaggerated pigmentation and other evidences of degenerative changes in the autonomic ganglion cells. According to Dolley and Guthrie (1918), the development of melanotic pigment in the ganglion cells of experimental animals (dog, rabbit) is always a result of functional depression of these cells. Pure experimental senility, in their animals, was not accompanied by pigmentation of the nerve cells; therefore, they regarded pigmentation of these cells in senility as the result of senile depression which is almost inevitable in the organism.

According to Pilcz (1895), the beginning of pigmentation of the autonomic ganglion cells in man may usually be observed during the second year of life. Lubimoff (1874) observed some pigmented cells in the autonomic ganglia in fetuses of five and seven months. Spiegel and Adolf (1922) found traces of yellow pigment in the autonomic ganglion cells in the new-born. They also pointed out that pigmentation of the ganglion cells is more common in the ganglia of the sympathetic trunks and prevertebral plexuses than in the cranial and enteric autonomic ganglia. Marked pigmentation of the ganglion cells in any part of the body, except in disease, is not observed commonly until the age of forty years.

The pigment observed in the autonomic ganglion cells in man is mainly of two kinds, viz.: (*a*) yellow lipid pigment which is at least partially soluble in alcohol, ether, and other fat solvents and reacts to fat stains, and (*b*) darker, more stable pigment which is highly insoluble (Pilcz, 1895; Obsersteiner, 1903; Marinesco, 1906). In addition to these pigments, Marinesco also described, in the spinal ganglion cells, certain eosinophile granules which he regarded as related to the yellow pigment, and certain cyanophile granules

which he regarded as related to the melanotic pigment. Spiegel and Adolf (1922) were unable to find either eosinophile or cyanophile granules in autonomic ganglion cells. Yellow pigment usually appears earlier than the darker pigment in the autonomic ganglion cells in man. As age advances, the majority of the pigmented autonomic neurons show only dark pigment.

The pigmented autonomic ganglion cells exhibit a wide range of variation in the distribution of pigment. In many of the cells, pigment occurs only in a narrow peripheral zone. In others, it is aggregated in a restricted portion of the cell body at the base of a dendrite or the axon. In occasional cells, it appears as a cap-shaped mass at the periphery of the nucleus. In certain cells, masses of pigment granules also occur occasionally in the cytoplasmic processes. Extracellular pigment granules also occur, particularly in ganglia in which the majority of the ganglion cells are heavily pigmented. Under certain conditions, *e. g.*, in cachexia and arsenic poisoning, pigment may be distributed quite uniformly throughout the cytoplasm and become so dense that the nucleus is obscured. A ganglion cell in this condition has the appearance of a mass of dark pigment (Spiegel and Adolf, 1922). Heavy pigmentation of the ganglion cells is also a fairly constant accompaniment of atrophy of the autonomic ganglia (Kahlden, 1896; Graupner, 1898; Laignel-Lavastine, 1903).

Not infrequently preparations of autonomic ganglia in which many of the ganglion cells contain a moderate amount of melanotic pigment, exhibit no other evidence of pathological changes. This may be regarded as evidence of a previous pathological condition involving functional depression of the cells in question, from which they have quite fully recovered. In other instances, even moderate pigmentation of the ganglion cells is accompanied by changes in the structure and distribution of the chromidial substance, probably indicating an existing pathological condition of these cells. Heavy pigmentation probably is always accompanied by other degenerative changes in the autonomic ganglion cells. Doubtless, many of these cells become functionless as the normal cytoplasmic constituents are replaced by pigment granules. In pyridine-silver preparations of heavily pigmented ganglia, many of the ganglion cells have the appearance of a compact mass of pigment granules from which no cytoplasmic processes can be traced. Obviously, such ganglion cells are no longer functional.

The genesis of pigment in nerve cells and the relation of the lipid and melanotic pigments to each other have been discussed extensively. Certain investigators (Pilecz, 1895; Rosin, 1896; Obsersteiner, 1903, 1909; Marinesco, 1909) have regarded pigment as a normal organic constituent of certain nerve cells. This opinion is based mainly on the common occurrence of pigment in certain por-

tions of the central nervous system in man, *e. g.*, the substantia nigra and locus cæruleus. Under normal conditions, the substantia nigra contains no pigment in the lower mammals (Dolley and Guthrie, 1918). Neither does it always contain pigment in man. Pilcz and Marinesco, both of whom traced the development of pigment in the substantia nigra in human material, do not agree regarding its age incidence, probably by reason of the fact that the material studied was pathological in varying degrees; and pigment was not present at the same age in all cases. If pigment is not a normal constituent of certain nerve cells in the lower mammals, it seems highly improbable that the corresponding cells in man should be naturally endowed with this apparently useless material.

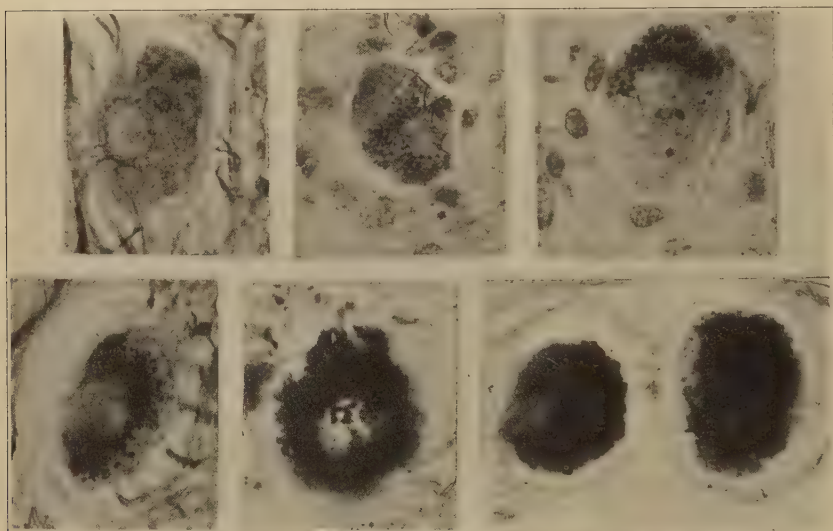


FIG. 67.—Autonomic ganglion cells (human), illustrating successive stages in pigmentation.

According to Hueck (1912), it is sometimes difficult to distinguish between melanin and lipoid pigments by reason of the fact that not infrequently they are intimately mixed and sometimes occur in the same granules. This finding in human material strongly suggests that these two types of pigment are closely related in origin. Still other investigators have regarded pigment in nerve cells as a normal product because it has frequently been observed in individuals who were apparently in good health. It must be borne in mind, however, that such relatively inert material as melanotic pigment may be retained in the cells long after the pathological process responsible for its origin has subsided and the cells in question have quite fully recovered.

That pigmentation of the nerve cells occurs more commonly in certain parts of the nervous system than in others is well known. The facility with which nerve cells acquire pigment seems to be correlated with the degree of differentiation of these cells. The autonomic ganglion cells exhibit a relatively low degree of differentiation. They also acquire pigment with relative facility. On the other hand, the Purkinje cells in the cerebellum are highly differentiated. Pigmentation of these cells is relatively uncommon (Marinesco, 1909; Hueck, 1912).

In an experimental study carried out on dogs and rabbits, Dolley (1917) found pigmentation of the Purkinje cells always associated with chronic depression. He never found pigment in these cells following acute depression of short duration. Neither was he able to produce pigmentation in these cells by stimulation ranging from normal activity to functional senility. Chronic depression alone resulted in pigmentation of the Purkinje cells in these animals. In another series of experiments, carried out on fowls, lipid pigment was observed in the Purkinje cells following acute depression. It should be recalled in this connection that lipid pigment does not occur in the dog and rabbit, since their fat is always lipochrome-free. In still another series of experiments carried out on dogs and rabbits, Dolley and Guthrie (1918) observed pigment in the nerve cells in various parts of the nervous system, including the superior cervical sympathetic ganglion. In these experiments also, pigmentation of the nerve cells was induced only by chronic functional depression. They, therefore, advanced the opinion that pigmentation of the nerve cells in the dog and rabbit is induced solely by functional depression.

The histogenesis of pigment in nerve cells probably is essentially similar to the histogenesis of pigment in various other cells. The derivation of pigment from intranuclear and extranuclear chromatin has been described repeatedly. Hertwig (1904) reported the transformation of extranuclear chromatin into pigment in *Actinosphaerium eichhorni* while in a state of functional depression. The depressed cells were in a condition of hyperchromatism; consequently, the transformation of chromidial material into pigment, under these conditions, may be regarded as a phenomenon of reorganization necessary for the restoration of the nucleus-plasma balance. Howard (1908) confirmed Hertwig's findings in the same species under similar conditions. He also observed the transformation of chromatin into pigment within the hypertrophied and hyperchromatic nucleus. Rösse (1904) reported the extrusion of nuclear material and its transformation into pigment in the cytoplasm in cells of a melanoma. Howard and Schultz (1911) also reported the occasional transformation of chromidial substance into pigment in tumors derived from unpigmented cells. In the dermal chromatophores

of various animals, according to Schultz (1912), the process of pigmentation begins in the undifferentiated mesoblastic cell by the extrusion of chromatin from the nucleus into the cytoplasm, resulting in the formation of a functional chromidial net. The chromatin in the cytoplasm later becomes transformed into pigment.

According to Dolley (1917) and Dolley and Guthrie (1918), the formation of pigment in the nerve cells in experimental animals in a state of functional depression involves both the intranuclear and extranuclear chromidial apparatus. They observed the transformation of chromidial material into pigment both in the nucleus and cytoplasm. Their findings strongly suggest that, in the animals used in their investigation (dog, rabbit), melanotic pigment arises in the nerve cells only from the chromidial substance, under the influence of chronic functional depression.

Species whose tissue fat is colored with the carotinoids, *e. g.*, the cow, horse, fowl, man, etc., carry the carotinoid pigments in the blood plasma. Fat absorbed by the cells, in these species, may carry in carotinoid pigment. Since nerve cells, like other tissue elements, absorb fat, the occurrence of lipoid pigments in these cells could be explained on this basis. The fact that lipoid pigment has been observed often in nerve cells, particularly in the young, strongly suggests that it may occur, in these cells, under normal physiological conditions. That its accumulation in the nerve cells is facilitated under certain pathological conditions is amply demonstrated. Dolley and Guthrie also advanced certain experimental data which indicate quite clearly that excessive deposition of fat in the nerve cells is a characteristic of functional depression.

Vacuolization.—The occurrence of vacuoles in occasional ganglion cells in sections of autonomic ganglia prepared by the usual methods need not be regarded as abnormal. Vacuolization of the autonomic ganglion cells in large numbers is usually associated with other degenerative changes in the cells and must be regarded as pathological. In some instances, small vacuoles occur which are separated from each other only by thin protoplasmic septa. The latter condition was observed by Spiegel and Adolf (1922) in a case of pemphigus vegetans. This observation is of especial interest by reason of the fact that in this disease the spinal ganglion cells undergo similar vacuolization. Vacuolization of the autonomic ganglion cells has also been observed in cases of advanced arteriosclerosis (Spiegel and Adolf, 1922; Stämmeler, 1923) and other chronic pathological conditions. Not uncommonly vacuolated cells also contain pigment, but no essential relationship of the vacuoles to the pigment has been pointed out. Many of the vacuoles apparent in sections of fixed material probably represent intracellular fatty inclusions.

Neuronophagia.—Neuronophagia of autonomic ganglion cells is not an uncommon phenomenon in both acute and chronic metabolic

disturbances in the autonomic ganglia. This may be either primary or secondary neuronophagia. Primary neuronophagia is brought about mainly by inflammatory infiltration which also affects the ganglion cell capsule; secondary neuronophagia, by changes in the ganglion cells which result in a chemotactic attraction of phagocytic elements. Clearly, only secondary neuronophagia can take place under physiological conditions. Neither need destruction of occasional autonomic ganglion cells by this process be regarded as abnormal, particularly after middle age. Empty cell capsules and capsules which contain only a remnant of the ganglion cell may be observed occasionally in preparations of autonomic ganglia which show little or no evidence of other pathological changes. Not infrequently, preparations of autonomic ganglia in which the majority of the ganglion cells are pigmented and exhibit changes in the chromidial substance also exhibit evidence of extensive neuronophagia. The destruction of the ganglion cells by secondary neuronophagia may be accomplished by cells derived from the endothelial lining of the ganglion cell capsule or by wandering phagocytic elements, usually small round cells, which are attracted into the cell capsule, depending on the type of metabolic disturbance in the autonomic ganglion cell.

Primary neuronophagia of autonomic ganglion cells is commonly associated with inflammation of the autonomic ganglia. In the initial stages of inflammation, the endothelial cells lining the ganglion cell capsules proliferate and the walls of the capsules become materially thickened. Some of the endothelial cells become separated from the wall of the capsule and lie free in the lumen where they assume the rôle of phagocytes and take part in the destruction of the ganglion cell. Inflammation of the autonomic ganglion results in its infiltration by lymphocytes and leukocytes. Many of these cells also penetrate the ganglion cell capsules and take part in the phagocytosis of the ganglion cells (Fig. 68). The phagocytic process may continue until the autonomic ganglion cell is completely consumed. After the inflammatory process has subsided, nothing remains in the lumen of the thickened capsule, in such cases, but amorphous material, colloidal masses and fragmented cells (Stämmeler, 1923).

According to Spiegel and Adolf (1922), neuronophagia, particularly the secondary type, is a more common phenomenon in the autonomic ganglia than in the central nervous system. This difference probably is correlated with the difference in the relationships of the neurons in the autonomic ganglia and the central nervous system respectively to the adjacent tissue. The neurons in the central nervous system are in a large measure protected against the injurious effects of metabolic disturbances by reason of the fact that the neuroglia cells play an important rôle in the removal of

injurious metabolites from them. The endothelial cells lining the ganglion cell capsules do not protect the autonomic ganglion cells in the same manner (Spiegel and Adolf, 1922).

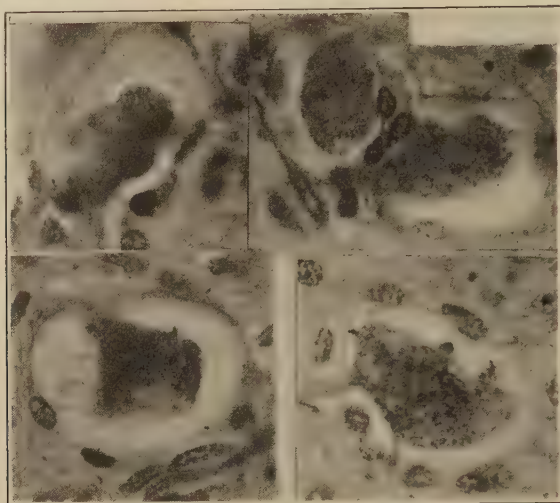


FIG. 68.—Autonomic ganglion cells (human) undergoing neuronophagia.

Other Degenerative Changes.—Hyalin degeneration of autonomic ganglion cells occurs not uncommonly under certain conditions. Shrinkage of the autonomic ganglion cells is also a common phenomenon, especially in senility and cachectic states. Shrunken ganglion cells usually also exhibit other pathological changes, *e. g.*, chromatolysis and pigmentation. The most heavily pigmented ganglion cells are not uncommonly shrunken to a relatively small mass. Shrunken ganglion cells in which the nucleus is not obscured by pigment also exhibit marked nuclear changes. The nucleus also becomes displaced toward the periphery of the cell body where it may cause appreciable bulging. In some instances, it is actually extruded from the cell. In silver preparations, the neurofibrillar structure also exhibits marked changes. The meshwork becomes coarser and the neurofibrils appear to be materially thickened. Later they undergo fragmentation and the cell body assumes a vacuolated or fenestrated appearance.

Changes in the Autonomic Nerve Fibers.—In contrast to the pathological changes observed in the autonomic ganglion cells, no well-marked pathological changes in the autonomic nerve fibers have been described. Preparations of autonomic ganglia exhibit a wide range of variation in the abundance of nerve fibers, but this does not afford a safe basis for any conclusion regarding the effect

of pathological changes in the ganglion cells or their fibers. Pyridine-silver preparations show clearly that the processes of many ganglion cells which contain a relatively large amount of pigment and also exhibit other degenerative changes, including thickening

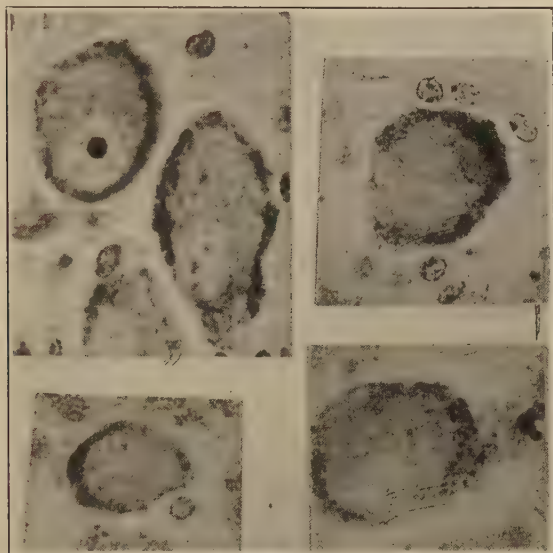


FIG. 69.—Autonomic ganglion cells (human), showing hyalin degeneration.

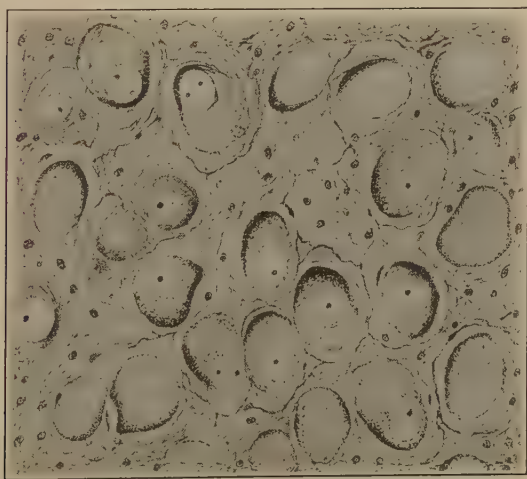


FIG. 70.—Drawing from a section of the celiac ganglion of a dog prepared three weeks after distilled water was injected into the ganglion. Practically all the ganglion cells show hyalin degeneration.

of the neurofibrils, are still intact. In many instances, an intact fiber may be traced from a ganglion cell which is obviously swollen and vacuolated and in which the nucleus has been displaced toward the periphery. On the other hand, it is impossible, in many cases, to trace any cytoplasmic processes from the most heavily pigmented and shrunken ganglion cells in preparations in which the processes of the majority of the ganglion cells are well impregnated. Silver impregnation methods are not well adapted to reveal initial pathological changes in nerve fibers. Neither have other methods been used extensively in investigations bearing on this problem. Nevertheless, certain meager observations regarding pathological changes in autonomic fibers have been recorded. Libimoff (1874) reported the occurrence of fat droplets in the unmyelinated nerve fibers in cases of pneumonia, carcinoma, and nephritis. Roux (1899) reported diminution in the number of the unmyelinated fibers of the smallest caliber (4 to 5 microns) in the cervical and thoracic sympathetic trunks and splanchnic nerves, but no diminution in the number of the larger myelinated fibers, presumably of spinal ganglion origin, in cases of tabes dorsalis. Graupner (1898) reported atrophy of the unmyelinated nerve fibers in cases of senility and tabes and in one case of exophthalmic goiter combined with diabetes mellitus. On the other hand, he claimed to have observed excessive development of the unmyelinated nerve fibers in two cases of exophthalmic goiter. More exact knowledge of pathological changes awaits further investigation.

Changes in the Interstitial Tissue.—That the interstitial connective tissue in the autonomic ganglia increases as age advances is well known. Preparations of ganglia taken from new-born or young children contain relatively little interstitial connective tissue, but the majority of the ganglion cells are closely aggregated, their capsules being separated only by a delicate connective tissue framework. Some of the cell capsules are separated somewhat farther by bundles of nerve fibers. The intraganglionic connective tissue framework is continuous with the connective tissue capsule of the ganglion. Preparations of autonomic ganglia taken from persons of middle age and older, in the absence of marked pathological changes, show a progressive increase in the amount of interstitial connective tissue, but, in most cases, the interstitial tissue does not become excessive. On the other hand, pathological conditions involving marked changes in the autonomic ganglion cells usually also result in a marked increase in the interstitial connective tissue. For example, in cases of senility with cachexia, the interstitial connective tissue becomes so excessive that most of the ganglion cell capsules are separated relatively widely from each other. In cases of arteriosclerosis, the autonomic ganglia exhibit excessive development of the interstitial connective tissue and marked thickening of

the adventitia of the arteries and veins (Stämmmler, 1923). As the interstitial connective tissue increases, the capillary blood vessels also increase in number. The findings in preparations of autonomic ganglia taken at autopsy in a wide variety of cases strongly suggest that all chronic pathological conditions which involve marked changes in the autonomic ganglion cells are accompanied by an abnormal increase in the interstitial connective tissue. That chronic infections which result in inflammation of the autonomic ganglia also result in hyperplasia of the interstitial connective tissue is well known. In a study of 100 cases following infectious diseases, Laignel-Lavastine (1905) observed hyperplasia of the interstitial connective tissue in all cases in which the infection had run a chronic course. Stämmmler (1923) reported pathological changes in the interstitial connective tissue in the autonomic ganglia in approximately 50 cases in which death resulted from infectious disease.

Hyperemia and infiltration of the autonomic ganglia, under pathological conditions, even in the absence of infection, is a common phenomenon (Stämmmler, 1923). Infiltration of the interstitial connective tissue in certain of the autonomic ganglia in senility and cachectic states was observed by Foa as early as 1874. This observation was confirmed by more recent investigators (Spiegel and Adolf, 1922; Stämmmler, 1923). The exact sources of the cells which invade the interstitial tissue, under these conditions, is not definitely known. They are identical in their staining reactions with lymphocytes and are usually more closely aggregated in proximity to the blood vessels than throughout the interstitial tissue (Spiegel and Adolf, 1922). These facts strongly suggest that they invade the tissue from the blood vessels, but do not prove their hematogenous origin. They may be derived at least in part from the vascular endothelium. Regardless of their origin, these cells must be regarded as wandering phagocytes which in many instances invade the ganglion cell capsules and take part in the phagocytic destruction of the ganglion cells. As indicated above, this process, in the absence of infection, must be regarded as secondary neuronophagia. In Sudan preparations, Spiegel and Adolf (1922) observed that many of the wandering cells in proximity to the blood vessels were laden with fat. This observation further supports the theory that the wandering elements in question are phagocytes and indicates quite clearly that they take part in the transportation of waste metabolites toward the blood vessels, thus facilitating their elimination through the blood stream.

Preparations of autonomic ganglia taken in cases of infectious disease, if not complicated by the changes described above, present quite a different histological picture. There may be little or no increase in the interstitial connective tissue, but, in many cases in which marked changes in the ganglion cells are not yet apparent,

there may be marked capillary hyperemia. This hyperemia is an important factor in the infiltration of the interstitial tissue. According to Stämmeler, hyperemia of the autonomic ganglia, in cases of infection, is commonly accompanied by abundant diapedesis of white cells which become aggregated in the perivascular lymph vessels and gradually invade the interstitial tissue throughout the ganglion. The invading cells are mainly lymphocytes and mononuclear leukocytes. Although neuronophagia may be evident, lymphocytes and leukocytes are not commonly found in large numbers within the ganglion cells capsules. Phagocytic destruction of autonomic ganglion cells is observed only rarely in cases of acute infection.

Although acute infectious diseases result in inflammatory reactions of the blood vessels and connective tissue framework of the autonomic ganglia and retrogressive changes in the ganglion cells which, in some instances, result in necrosis of many of these cells, the infecting organisms are rarely observed in the autonomic ganglia. In preparations taken from a wide variety of infectious cases, Stämmeler (1923) observed bacterial organisms in the autonomic ganglia in but a single case, viz.: a case of streptococcus septicemia. He concluded, therefore, that the primary degenerative changes in the autonomic ganglion cells represent reactions to toxic substances and that these reactions call forth secondary inflammatory reactions in the ganglia.

Although inflammatory reactions in the autonomic ganglia and degenerative changes in ganglion cells have been observed in a wide variety of infectious diseases, Stämmeler (1923) found such changes most frequently in cases of general streptococcus, staphylococcus, and pneumococcus infections. The extent of the damage to the autonomic ganglion cells also varies widely. In most cases, relatively few ganglion cells exhibit such marked changes that they must be regarded as necrotic or beyond the possibility of recovery. In a small percentage of the cases in Stämmeler's series, the majority of the ganglion cells were obviously necrotic.

THE FUNCTIONAL SIGNIFICANCE OF PATHOLOGICAL CHANGES IN AUTONOMIC GANGLION CELLS.

Our present knowledge of the pathology of the autonomic nervous system is based mainly on observations made on human material obtained at autopsy. Such material affords little opportunity for the study of the progress of pathological processes. Although some experimental data are available, the progress of pathological changes in autonomic ganglion cells from the incipient stages to the end-result has not been described in such detail as in certain types of neurons in the central nervous system. In general, the pathological

changes described in the autonomic nervous system, in so far as they involve the nuclear and cytoplasmic constituents of the ganglion cells, are similar to changes described in the central nervous system. It may be assumed, therefore, that pathological changes in nerve cells are comparable in their effect on the functional capacity of the cells, although the phenomena involved differ in degree in the various types of nerve cells, depending on their degree of specialization and their nutritive relationships to adjacent supporting cells.

The results of the extensive experimental studies carried out by Dolley and his students, cited above, show clearly that the pathological changes induced in the central nervous system, particularly in the Purkinje cells, in animals by means of excitant and depressant stimuli, involve primarily the chromidial apparatus and the nucleus-plasma ratio. They also indicate quite clearly that stimulation and depression constitute the major factors in the genesis of pathological changes in nerve cells. Verworn regarded excitation and depression of nerve cells as quantitative opposites in the physiological sense. According to Dolley (1914), they are quantitative opposites also in regard to their reciprocal mass relations. Excitation finally results in a change in the nucleus-plasma ratio in favor of the cytoplasm; depression results in a change in favor of the nucleus. Excessive cellular activity depletes the available chromatin supply and in exhaustion chromatin formation fails; in depression, chromatin formation is inhibited. "In both cases," according to Dolley, "the phenomena of function disturbed by fatigue depend upon the state of the same substance, which in both ultimately reaches the same state of total deficiency. For the same reason irritability is progressively lowered in both prior to the total cessation of function." In 1916 he wrote: "The end of excitation is organic exhaustion. Complete exhaustion must be accompanied by loss of function. Depression is a blocking of function, its performance on a lower level. When depression is complete there is also loss of function. Though the end-result is reached by entirely different processes, and is subtended by diametrically opposite constitutions, it is identical for either process in a complete functional incapacity. The exhausted cell is just as incapable of function as an absolutely depressed cell. In the one case the cell has no materials to work with, in the other it cannot use what it has." In view of the fact that all stimuli must be classified physiologically as pure excitants, pure depressants, or stimuli which first excite and later depress, and on the basis of his histological findings, Dolley concluded that "between the two opposite phases, activity and depression, activity, incited by excitatory stimulation and ending in organic fatigue, is primordial and plays the vaster rôle in health and disease."

Although exact data regarding the effect on visceral functions of stimulation or depression associated with pathological changes in the autonomic ganglion cells, either in the early or later stages, are not available, it is well known that tonic changes either in the sympathetic or parasympathetic nerves may profoundly affect the functional state of the visceral organs. No pathological changes in the autonomic nervous system may, therefore, be regarded as without functional significance. Although pathological processes rarely affect all the neurons in a given autonomic ganglion in the same degree, it can hardly be assumed that the excitant or depressant stimulus involved does not affect all of them in some degree. Furthermore, as the pathological process advances, many of the ganglion cells must become functionally exhausted or completely depressed. Although reserve cells may be available, cessation of function on the part of any considerable percentage of the autonomic ganglion cells must profoundly affect the functional state of the organs in question.

CAPACITY FOR RECUPERATION.

Experimental data regarding the capacity of damaged autonomic ganglion cells for recovery are not available. The consensus of opinion seems to be that the autonomic ganglion cells possess the capacity for regeneration of any part of the cell body only in a limited degree. Yet, their capacity for regeneration is far greater than that of the more highly specialized neurons in the central nervous system. That they possess the capacity for recovery following exhaustion or depression within relatively wide limits seems highly probable. According to Dolley (1911), the power of recovery from exhaustion is an inherent capacity of nerve cells, although it varies in each individual after the same degree of exhaustion. According to his findings in the Purkinje cells in experimental animals, the chromatin equipment of the cell affords a valuable index of its capacity for recuperation. In his experiments, the best recoveries showed rapid restoration of chromatin. In those cells which made the poorest recoveries, chromatin restoration was delayed and the chromatin content remained scanty. In very young animals (dogs), the Purkinje cells were affected more profoundly by the same strain and recovered more slowly than in adult animals. In another series of experiments, Dolley (1917) was able to show that the Purkinje cells also possess the capacity for recovery after depression in a comparatively greater degree than after exhaustive activity, probably because excessive excitation depletes the nuclear chromatin to a greater extent than depression. Yet, depression which goes too far, like complete exhaustion, results in permanent disorganization of the cell. "There is no rejuvenes-

cence of the nerve cell," according to Dolley, "but only a recovery which whether from depression, disease atrophy or exhaustion, involves the regrowth of the same preëxisting substances."

A direct application of findings in the central nervous system to the autonomic nervous system, in the absence of corroborative evidence, is unwarranted. Yet, inasmuch as the autonomic ganglion cells are more primitive and less highly differentiated than the Purkinje cells, it may be assumed that the former possesses the capacity for recovery following exhaustion or depression at least in the same degree as the later.

THE RELATION OF PATHOLOGICAL CHANGES IN THE AUTONOMIC GANGLIA AND GANGLION CELLS TO DISEASE.

Statement of the Problem.—The data set forth above show clearly that many pathological conditions including both acute and chronic infectious diseases and non-infectious intoxication, are commonly accompanied by changes in the autonomic ganglia, and more particularly in the autonomic ganglion cells, which must also be regarded as pathological. The question naturally arises, are the pathological changes in the autonomic ganglia merely accompaniments of disease processes, brought about by the same causes which gave rise to the disease in question, or is there a causal relationship between the disease process and the accompanying pathological changes in the autonomic ganglion cells? The further question also arises, may not pathological changes in the autonomic ganglion cells which are either induced by a disease process or arise simultaneously with it become causative factors in the production of other simultaneous or subsequent pathological processes? These questions are of far-reaching importance both physiologically and clinically, but the data available at present do not afford an adequate basis for their solution in all cases.

General Effect of Autonomic Lesions on the Course of the Associated Disease.—That pathological changes in the autonomic ganglion cells are, in many instances, either induced by the cause of the disease with which they are associated or arise as a result of the disease process is quite clear. Obviously, the pathological changes which arise in the autonomic ganglia and ganglion cells during the course of an infectious disease must be regarded as a result and not as a cause of the disease process. They are referable mainly to the direct effect of intoxication and metabolic disturbances, including inflammatory reactions in the ganglia. Yet, in many cases, they play an important rôle in the course and termination of the disease by reason of their stimulating or depressing effect on the nerves through which the regulatory nervous control of the visceral functions is mediated. For example, continued stimulation

of the sympathetic or depression of the parasympathetic innervation of the gastro-intestinal canal results in chronic constipation. On the contrary, depression of the sympathetic or stimulation of the parasympathetic innervation of the stomach and intestine results in hypermotility of the gastro-intestinal musculature.

Not a few investigators have called attention to the clinical importance of the effect on the vasomotor apparatus of changes in the sympathetic ganglion cells brought about during the course of infectious diseases. On the basis of extensive histological data, particularly the results of Mogilnizky's (1923) studies, bearing on the relation of pathological changes in the autonomic ganglia to infectious diseases, Abrikossoff (1923) pointed out that those infectious diseases in which the symptoms referable to depression of the vasomotor apparatus are most marked are also accompanied by the most marked degenerative changes in the autonomic ganglion cells. On the other hand, certain infectious diseases are usually not accompanied by marked vasomotor disturbances even though many of the autonomic ganglion cells undergo pathological changes.

Chronic infections as well as repeated acute infections and other forms of intoxication invariably result in necrosis of many autonomic ganglion cells and less extensive damage to others, resulting in impairment of function of the autonomic nervous system in a greater or lesser degree. Although it must be assumed that the autonomic ganglion cells possess the capacity for recuperation within relatively wide limits, it is not inconceivable that even moderate pathological changes in these cells may result in changes in their reactivity of relatively long duration. Doubtless, many visceral neuroses have their origin in functional impairment of the autonomic nervous system. The finding by D'Amato and Marci (1905) of chronic parenchymatous and interstitial inflammation of the enteric ganglia in cases of gastritis is in full accord with this assumption. On the basis of extensive clinical studies, Laignel-Lavastine also expressed the opinion that many of the neuroses of the gastro-intestinal canal have their histopathological substratum in impairment of the autonomic nervous system. That pathological lesions of the autonomic nervous system play an important rôle in the genesis of arteriosclerosis has also been maintained on the basis of extensive clinical and experimental findings (Stämmli, 1923; Danisch, 1928; and others).

NEOPLASMS OF THE AUTONOMIC NERVOUS SYSTEM.

True nerve tumors, *i. e.*, neoplasms which consist of nervous tissue elements, occur relatively infrequently, but are more common in the autonomic than in the central nervous system. They are also more common in the sympathetic than in the parasympathetic

division. Neoplasms of the autonomic nervous system include both benign and malignant growths, but their clinical manifestations are not well known. In most of the cases reported, the neoplasm was not recognized clinically, but was discovered at autopsy and usually regarded as a purely secondary finding. Malignant neoplasms of the autonomic nervous system occur almost exclusively in infants and young children. Benign tumors of the autonomic system may occur at any age. The fact that they are not usually recognized clinically suggests that they exist without giving rise to marked symptoms. In most cases, neither the patient nor the physician is aware of their presence. In some instances, benign tumors of the autonomic nervous system give rise to symptoms mainly by reason of their mechanical effect, which may warrant surgical interference.

Neoplasms of the autonomic nervous system may be classified as (1) neurocytomata, (2) neuroblastomata, (3) sympathoblastomata, (4) ganglioneuromata, (5) paragangliomata, and (6) neurofibromata. These neoplasms are all closely related ontogenetically. All the cellular types not only merge almost imperceptibly into one another, but cells in all stages of development may also occur in the same tumor. Furthermore, neurofibromatosis may be combined with any of the other types of tumor formation.

Neurocytoma.—The neurocytoma consists mainly of undifferentiated cells of nervous origin. Marchand (1907) reported a tumor of this type in a man, aged fifty-six years, which he described as a neurocytoma of the Gasserian ganglion. According to his description, it was composed of undifferentiated round, oval, or polygonal cells with homogeneous cytoplasm and a large vesicular nucleus. No fibrillar structure was apparent in the ground substance. Wright (1910) pointed out that the cells composing neoplasms of this type are neurocytes in the undifferentiated stage. In some instances, the ground substance reveals delicate fibrils which do not react either like neuroglia, collagenous fibers, or fibroglia to Mallory's stain; therefore, they resemble the fibrillæ which occur in the primordia of the autonomic nervous system. Both the cells and fibrillæ in the tumor exhibit the same morphological characters and arrangement as the cells and fibrils in the autonomic primordia and adrenal medulla. The fibrils tend to run in parallel bundles with which characteristic aggregates of cells are associated. Wright also observed ball-like structures composed of two or three concentric rows of nuclei surrounding a central meshwork of delicate fibrils in preparations of these tumors. These structures conform to the rosettes described by Kuster (1905) in preparations of neuroblastomata. They are, however, not morphologically identical with the rosettes which are characteristic of the glioma. Inasmuch as undifferentiated cells of nervous origin (indifferent cells) migrate

from all parts of the central nervous system, Wright advanced the opinion that neurocytomata may occur in any part of the body. Having himself recognized four tumors of this type in a single year, he also concluded that neurocytomata occur more frequently than the reported cases would seem to indicate.

Neuroblastoma.—The neuroblastoma is a malignant neoplasm which may involve any part of the nervous system, but occurs most frequently at the site of a sympathetic ganglion, in the adrenal medulla, or elsewhere behind the peritoneum, whence it commonly metastasizes to the liver, skeletal system, and lymph nodes. It is composed mainly of neuroblasts which tend to become arranged in solid masses of fibrils (Kuster's rosettes). Fibrils are usually present in the ground substance, although some tumors of this type exhibit very little fibrillar differentiation. As pointed out by Landau (1913), the fibrils only represent a degree of differentiation of the cells. If the cells remain in the early phases of neuroblast differentiation, fibrils are scarcely apparent and the tumors may present a histological picture similar to that of a lymphosarcoma, but if cell differentiation has advanced beyond the earliest neuroblast stages the fibrils are more numerous. In general, the degree of differentiation of the cells in these tumors is correlated with age. The great majority of the neuroblastomata reported have occurred in infants or young children. Meunier (1927) recently reported the occurrence of a typical sympathetic neuroblastoma in a girl, aged six and a half years. The younger the patient the less differentiated are the cells and the more malignant is the neoplasm. Landau emphasized the direct relation of the tissue differentiation, the character of the growth, and the age of the host, to each other. If the host survives, tissue differentiation increases with age, while malignancy decreases and the growth assumes the appearance of a malformation. Most of the neuroblastomata of the differentiated type contain cells in various stages of differentiation, but either the undifferentiated or the more differentiated type predominates. Foci of indifferent cells may also be present. Differentiated cells occur, but less frequently, in the undifferentiated neuroblastomata. Indeed, neuroblastomata may exhibit any combination of differentiated and undifferentiated cells (Wahl, 1914).

• **Sympathoblastoma.**—The sympathoblastoma represents a somewhat later stage in the differentiation of sympathetic nerve cells than the neuroblastoma. It is a malignant neoplasm, occupying a position midway between the undifferentiated neuroblastoma and the ganglioneuroma, and is composed mainly of cells which have become differentiated beyond the neuroblast stage. Martius (1913) described a neoplasm of this type in the cervical sympathetic of a boy, aged two and a half years. It was made up mainly of cells which were somewhat larger than neuroblasts and contained relatively large oval nuclei.

Ganglioneuroma.—The ganglioneuroma represents a still later stage in the differentiation of nerve cells. It consists mainly of ganglion cells and fibers. The ganglion cells exhibit a wide range of variation both in size and general morphology. Many of them are relatively small round cells which, in their general appearance, have little in common with normal ganglion cells, yet their nervous origin is indicated by the vesicular character and meager chromatin content of the nucleus and the character and arrangement of the chromidial bodies in the cytoplasm (Oberndorfer, 1907; Pick and Bielschowdsky, 1912). The larger cells show all the characters of ganglion cells. Many of them are binuclear or polymorphonuclear. Degenerative changes in the cytoplasm are not uncommon. Many of the cells also contain pigment. According to Oberndorfer, the ganglion cells are not enclosed in capsules. Others have described ganglion cell capsules in some instances. Many of the ganglion cells show multiple processes in which, as well as in the cell body, neurofibrils can be demonstrated, especially by silver impregnation methods. Pericellular meshworks of fibers have also been observed (Fuchs, 1924). The fibrous components of the tumor include both myelinated and unmyelinated nerve fibers, but the latter usually predominate. The myelinated fibers not infrequently show evidence of degeneration. The myelin sheath may be fragmented or it may show varicose swelling.

In general, the ganglioneuroma may be regarded as a benign tumor. It is usually definitely delimited and does not infiltrate or metastasize. It may become malignant only if it includes groups of immature or undifferentiated cells. In such cases, infiltration and metastasis may take place. Malignant ganglioneuromata have been reported mainly in young persons. The younger the patient, the more undifferentiated are the cells and the more apt is the ganglioneuroma to become malignant (Falk, 1907). Tumors of this type may occur at any age, but are most common in children and young adults, and are rarely found after the age of forty years.

Paraganglioma.—The paraganglioma is a relatively rare benign tumor composed of chromaffin cells. It may occur wherever chromaffin tissue exists, but is found most commonly in the adrenal medulla and carotid gland. Since the chromaffin tissue arises from cells which become displaced from the central nervous system with the cells which give rise to the sympathetic primordia, the paraganglioma is also genetically related to the other neoplasms of the autonomic nervous system. These tumors are relatively small and are, as a rule, discovered in middle aged and elderly persons, being found sometimes accidentally at autopsy. Not infrequently they are associated with neurofibromatosis. Inasmuch as the cells composing the paraganglioma represent fairly mature chromaffin cells, this tumor corresponds to the ganglioneuroma.

Tumors made up of immature chromaffin cells are not known.

Most paragangliomata, however, exhibit a wide range in the degree of differentiation of the chromaffin cells. The majority of the cells are large epithelium-like elements, which often contain adrenalin and glycogen. Many of these cells assume a characteristic brown color after fixation with chrome salts. Those which do not react in this manner to chrome salts probably are not yet fully differentiated. Although these tumors are made up mainly of chromaffin cells which appear as polymorphous or polyhedral elements with finely granular vacuolated cytoplasm, transitional forms, multinucleated giant cells, ganglion cells, and cystic or hemorrhagic areas are often observed. Myelinated or unmyelinated nerve fibers are also encountered occasionally (Herxheimer, 1914).

Neurofibromatosis.—Neurofibromatosis involves mainly the peripheral nerves. It is frequently characterized by the appearance of multiple tumors in the subcutaneous tissue, areas of pigmentation, and less often by a condition resembling elephantiasis (elephantiasis neuromatosa). According to von Recklinghausen's original conception, these tumors are derived exclusively from the perineurium and endoneurium, *i. e.*, they are mesodermal in origin. Verocay (1908) and others have shown, however, that in certain cases neurofibromatous growths exhibit very little connective tissue, but are made up mainly of nerve fibers. Verocay assumed that the newly-formed nerve fibers are derived either from the neurilemma or undifferentiated embryonic nerve cells. Other investigators have shown that tumors of this type involve both hyperplasia of the connective tissue and new growths of nerve fibers (Fuchs, 1924).

In isolated cases, neurofibromatosis has been observed in the autonomic nervous system. Askanazy (1907) described tumors between the longitudinal and circular muscles in the gastro-enteric canal in which he found ganglion cells and nerve fibers. Obviously, these tumors involved the myenteric plexus. In rare instances, fibromatosis of the nerves supplying the bladder and seminal vesicles have also been reported (Fuchs, 1924). Roux (1926) described neurofibromatosis involving the sympathetic fibers accompanying the arteries in the pelvic region in certain cases of sclerous and cystic degeneration of the ovaries accompanied by dysmenorrhea and other pelvic disorders. Brocher (1927) recently reported three cases of neurofibromatosis in the autonomic nervous system. In one of these, the growth involved the myenteric plexus near the cardiac end of the stomach. In another, it involved the entire left sympathetic trunk from the upper end of the common carotid artery to the promontory of the sacrum. In the third case, only the thoracic portion of the left sympathetic trunk was involved. In all three cases, the neurofibromata were discovered as purely secondary findings at autopsy.

Nicolaysen (1921) and Askanazy (1921) called attention to alterations in the nerves adjoining gastric ulcers which are not

always destructive, but, on the contrary, exhibit a marked tendency toward proliferative, degenerative activity. The changes in the nerves in the vicinity of gastric ulcers were studied in detail in an extensive series of cases by Okkels (1927). According to his findings, the proliferative alterations of the nerve tissue constitute a central cicatrix neuroma, which may originate in the myenteric plexuses or periarterial nerves. The former contain nerve cells; the latter are devoid of nerve cells. These alterations are not specific for gastric ulcer; consequently, they may be regarded as secondary.

PATHOLOGICAL CHANGES IN THE AUTONOMIC CENTERS IN THE CENTRAL NERVOUS SYSTEM.

The Intermediolateral Cell Column.—Changes in the neurons in the intermediolateral cell column in the spinal cord which were interpreted as pathological have been described by not a few investigators. Laignel-Lavastine (1903) reported degenerative changes in these cells following section of the splanchnic nerves and other communicating rami. De Buck (1904) reported pathological changes, including chromatolysis, in the neurons in the intermediolateral column in the third, fourth, and fifth sacral segments following resection of the rectum. Irimesco and Pahron (1905) reported similar changes in the neurons in this column in the sacral segments following suppuration and gangrene in the pelvis minor. Jacobsohn (1908) reported advanced degeneration of the neurons in the intermediolateral cell column in the upper thoracic segments in a woman with carcinoma involving the brachial plexus. This condition was accompanied by constriction of the pupil and narrowing of the rima oculi on the same side. Marinesco and Parhon (1908) reported a somewhat similar case in which a carcinomatous growth making pressure on the brachial plexus was accompanied by oculo-pupillary disturbances on the same side, although the pathological changes in the cells in the intermediolateral column were less extensive. They also reported chromatolysis and atrophy of the upper levels of the intermediolateral cell columns following section of both cervical sympathetic trunks.

Diseased conditions of the spinal cord, *e. g.*, tumors, cavities, and inflammatory processes, also give rise to disturbances of visceral functions by reason of their effect on the neurons in the intermediolateral column. In cases of poliomyelitis, muscular paralysis is accompanied by vasomotor disturbances and local disturbances in the secretory activity of the sweat glands. In this disease, the inflammatory process in the spinal cord may involve the intermediolateral cell column directly, but not infrequently pathological changes also occur in the corresponding ganglia of the sympathetic trunk. In some instances, syringomyelia is also accompanied by scleroderma and pupillary disturbances, probably by reason of

encroachment of the spinal cord lesion on the intermediolateral cell column (Buscher, 1924).

Visceral disturbances resulting from localized lesions of the spinal cord probably are due, in most instances, to the effect of the lesion on the preganglionic neurons in the intermediolateral cell column. It does not follow, however, that the cell groups in question constitute the central autonomic centers through which the regulatory control of any given visceral function is mediated. The disturbance of function probably is the result of stimulation of the visceral neurons or interference with the efferent conduction of visceral impulses.

Autonomic Centers in the Medulla Oblongata.—Pathological changes in certain of the visceral nuclei in the medulla oblongata have also been reported. Marinesco (1897), Molhant (1910), and Brugsch, Dresel, and Lewy (1920) described changes in the neurons in the dorsal vagus nuclei following vagus section or extirpation of an organ innervated through the vagi, which they regarded as indicating retrograde degeneration of these cells due to section of their axons. Ceelen (1917) described a wide range of degenerative changes, including cell necrosis, in the region of the vasomotor center in the medulla oblongata, in cases of chronic nephritis. On the basis of his findings in these cases, he advanced the opinion that, in cases of chronic renal disease, toxic substances are thrown into the blood stream which exert a selective influence on the neurons in the vasomotor center through which they are kept in a constant state of stimulation.

Autonomic Centers in the Mid-brain.—That certain diseases which involve the mid-brain (encephalitis, hemorrhage, tumors) give rise to pupillary disturbances is well known. These disturbances are brought about by the effect of the mid-brain lesion on the preganglionic components of the oculomotor nerves, but little is known regarding pathological changes in these neurons or their relationship to specific mid-brain lesions.

Autonomic Centers in the Diencephalon.—The visceral centers in the diencephalon are located mainly in the hypothalamus and in relation to the walls of the third ventricle (Chapter III). That lesions in this portion of the brain give rise to profound visceral disturbances is well known. Experimental data which show clearly that lesions of the diencephalic autonomic centers may result in diabetes insipidus, vasodilatation, disturbances of the temperature-regulating mechanism, including the secretory activity of the sweat glands, disturbances in carbohydrate metabolism, and changes in the pupillary reactions are not wanting. Yet, little is known regarding histopathological changes in the autonomic centers in the diencephalon. Neither can any given symptom complex or disease entity be definitely correlated with a known pathological lesion in the diencephalon.

CHAPTER XVII.

VISCERAL SENSITIVITY AND REFERRED PAIN.

GENERAL STATEMENT.

SENSATIONS resulting from stimuli applied at the external surface of the animal organism and impulses received through its distance receptors play a major rôle in the reactions of the organism to environmental factors and in its adjustment to the external environment as a whole. Sensations resulting from stimuli arising within the body play an equally important rôle in the adjustment of the organism to its internal environment. Inasmuch as the visceral organs are not normally subjected to the stimuli which constantly play upon the surface receptors, they are, in general, insensitive to these forms of stimulation, *i. e.*, the reactions called forth in the visceral organs do not affect consciousness. On the other hand, adequate visceral stimuli give rise to sensations. In some instances such sensations are more or less definitely localized in the organ stimulated; more commonly they are not localizable or, if localizable, they are referred to a somatic or a visceral area removed from the point of stimulation.

In general, the visceral organs, including the central nervous system, are not sensitive to mechanical, chemical, thermal and electrical stimulation in the ordinary sense, *i. e.*, the application of these stimuli to the visceral organs, with certain exceptions, does not give rise to sensations. On the basis of experimental and clinical observations, certain investigators, notably Lennander and Mackenzie, denied the possibility of painful sensations referable to any of the internal organs which are innervated solely through the autonomic nervous system, unless the stimulation is of such a nature that it spreads beyond the area of autonomic innervation and affects afferent components of the somatic rami of the spinal nerves. Lennander (1906) even advanced the hypothesis, that all the internal organs which are innervated solely through the sympathetic nerves and the vagi, distal to the origin of the recurrent laryngeal nerves, are devoid of pain. Through the results of more recent studies, both experimental and clinical, it has become clear that disturbances in the internal organs may give rise to afferent impulses which are conveyed to the central nervous system through the visceral afferent components of the spinal nerves and give rise to painful sensations which are referable to the organ in which the stimulus arises. Likewise, adequate physiological stimuli, *e. g.*,

hunger contractions of the stomach, give rise to afferent impulses which are conveyed to the central nervous system in the same manner and give rise to sensations which in general are referable to the stomach. Yet, the great majority of the afferent impulses arising in the visceral organs under physiological conditions, though conveyed to centers in the central nervous system through which they play a part in the reflex regulation of visceral functions, do not reach the threshold of consciousness.

The production of sensations is conditioned by the character of the stimulus and the tissue on which the stimulus acts. As stated above, the visceral organs are, in general, insensitive to the majority of the stimuli to which the somatic tissues respond more or less acutely. Exaggeration of any of these stimuli in the somatic tissues results in painful sensations which are usually definitely localized. In general, pain is elicited in the visceral organs only in response to a vital process. That manipulation, pinching, cutting or tearing of the visceral organs give rise to no sensations has been abundantly observed during operative procedures. In the application of any mechanical stimulus it may also be observed that on passing from the skin into any of the orifices, *e. g.*, the mouth, there is a gradual diminution in sensitiveness as the area stimulated becomes farther removed from the external surface. Passing from the mouth down the digestive tube, sensitivity is lost at some level of the esophagus. Passing from the skin around the anus into the rectum, mechanical stimulation elicits no response beyond the line which separates the skin from the mucous membrane. Viewing the matter broadly, it may be stated that stimulation, by the ordinary methods, of the tissues which are innervated through the cerebrospinal nervous system gives rise to sensations, while stimulation of the tissues which are innervated solely through the autonomic nervous system does not. In the investigations bearing on this problem it has almost invariably been found that when pain was produced by mechanical stimulation, the stimulus affected tissues which are supplied by sensory cerebrospinal nerve components not incorporated in the autonomic nerves. This may be illustrated by the effects of stimulation of the serous membranes. According to Mackenzie (1922), the visceral layer of the tunica vaginalis of the testis is the only serous membrane which is sensitive to mechanical stimulation. It is also the only serous membrane which is known to be supplied by a cerebrospinal nerve. It receives a twig from the genital branch of the genito-femoral nerve. The parietal layers of the pleura and peritoneum are, in general, regarded as sensitive. The visceral layers of these membranes and the serous surface of the parietal layers are not sensitive. The outer surface of the parietal layers is sensitive by reason of the sensory cerebrospinal nerve fibers which supply that surface in abundance.

According to Mackenzie, the vital processes which produce visceral pain involve the contraction of smooth muscle. He was unable to demonstrate the production of pain in any other visceral tissue. Neither is pain produced by the mechanical stimulation of smooth muscle, but only when the muscle contracts in a peculiar manner. The normal functioning of all the hollow organs involves the contraction of smooth muscle, but, under physiological conditions, this does not generally give rise to sensations. When stimulated to contract in a particular way, as when the contractions become violent or spastic, or under circumstances in which the blood supply to the muscle is greatly diminished, the contraction of smooth muscle gives rise to pain. Mackenzie, therefore, regarded the contraction of smooth muscle as the major factor in the production of visceral pain.

Although the production of pain in other visceral tissues, in which the contraction of smooth muscle can be definitely ruled out as a contributing factor, has not been clearly demonstrated, it seems not improbable that visceral processes other than the contraction of smooth muscle may produce visceral pain. Under certain conditions, pain associated with hyperalgesia of the body wall may be regarded as an example of pain of this kind. Hyperalgesia probably may be caused by lesions of tissues other than muscle. It is clearly impossible, however, in many instances, to rule out the contraction of smooth muscle as a contributing factor.

In general, muscle pain differs from other pains in that it is wave-like in character, *i. e.*, it arises gradually, reaches a maximum intensity, and subsides gradually. The periods may last but a few seconds or many hours. Uterine pain, for example, illustrates all degrees of intensity and duration. Pain due to other causes, *e. g.*, the pain associated with hyperalgesia of the skin in engorgement of the liver, is usually not wave-like, but more or less continuous in character. In lingering muscle pains, the wave-like character is not infrequently obscured.

THE SENSITIVITY OF THE VISCERAL ORGANS.

Respiratory Organs.—That stimulation of the epithelium of the upper respiratory passages may give rise to sensations is well known. Irritation of any part of the respiratory epithelium may call forth reflex reactions which affect consciousness. The sensations in question are, however, not essentially visceral in character. That the lungs are insensitive to injurious or destructive influences is a fact of common clinical observation. Neither lacerating wounds nor disease processes which involve destruction of the lung tissue give rise to pain within the organ. Neither do inflammatory processes in the lungs give rise to localized pain unless they involve

the parietal pleura. That inflammation of the latter tissue gives rise to acute pain is also a fact of common clinical experience. Obviously, the nerve fibers which convey the afferent impulses involved to the central nervous system are the sensory cerebrospinal fibers which terminate in the deeper layers of the parietal pleura or the subpleural connective tissue. This acute pain usually subsides after a few days, even though involvement of the parietal pleura is still indicated by the physical findings. It is also significant that the acute pain accompanying pleuritic inflammation subsides rapidly with the accumulation of an exudate.

That the parietal pleura is highly sensitive to stimuli which affect the receptors in its deeper layers or the subpleural tissue is amply demonstrated. It has not been demonstrated beyond question, however, that sensations arise from stimuli which affect only its serous surface. Slight friction on this surface, according to Simenauer (1927), in most cases, does not give rise to sensations, and friction which gives rise to pain is felt most intensely along the course of the intercostal nerves. In Simenauer's experiments, pricking of the parietal pleura and moderate pressure on its serous surface were usually felt as such. Irritation of the central area of the diaphragmatic pleura commonly resulted in shoulder pain. All the data available at present regarding the effects of stimulation of the visceral pleura seem to warrant the conclusion that no impulses arise in this membrane which reach the threshold of consciousness (Hoffmann, 1920; Müller, 1924; Simenauer, 1927).

Circulatory Organs.—The Heart.—The normal activities of the heart give rise to no sensations, although in many instances the impact of the apex against the thoracic wall may be distinctly perceived by the palpating hand. It may be assumed that the portion of the thoracic wall in question has become so accustomed to the normal impact of the heart that it no longer gives rise to impulses which reach the threshold of consciousness. Whenever the action of the heart becomes exaggerated, as by physical exercise or emotional disturbance, the beating of the heart becomes clearly perceptible. Whether the sensations involved are the result of impulses arising in the heart or the thoracic wall is not easy to determine. In some instances the sensations seem to be referable to the heart. This is true especially in cases of paroxysmal tachycardia in which patients not uncommonly interpret their sensations as due to the contraction of the heart musculature. Not uncommonly patients also experience a feeling of inadequate heart action and "heart flutter." In other instances, the sensations which accompany exaggerated heart action are clearly referable to the thoracic wall. Such sensations probably result from impulses arising in the thoracic wall due to the unusual impact of the apex beat. It should be stated, however, that in many instances exag-

gerated or irregular heart action gives rise to no sensations. This is the case especially in chronic cardiac conditions. Not uncommonly a patient with chronic cardiac disease is quite unable to form an accurate judgment regarding his own cardiac activity.

That injuries to the heart and inflammation of the cardiac muscle give rise to no sensations, which are referable to the heart itself, is quite generally conceded. Neither is the endocardium sensitive to stimulation. Inflammation or even ulceration of the endocardium gives rise to no sensations. Frequent failures to recognize even ulcerative forms of endocarditis attest to the fact that such conditions may exist without giving rise to symptoms directly referable to the heart. On the other hand, endocarditis sometimes gives rise to discomfort, such as a feeling of pressure in the cardiac region, palpitation of the heart, and dyspnea. These sensations are not due to impulses arising in the endocardium, however, but rather to impulses arising by reason of impaired circulation.

Regarding the pericardium, it may be stated that there are no data available at present which indicate that impulses arising in this tissue ever reach the threshold of consciousness. Both the visceral and parietal pericardium probably are devoid of sensations. Pericarditis may exist in the absence of any symptoms referable to the heart. In severe cases of pericarditis, disturbances occur which give rise to sensations of pressure in the cardiac region, and not infrequently to shortness of breath and a feeling of anxiety. These sensations are not the result of impulses arising at the seat of the inflammatory process, however, but are manifestations of impaired heart action or pressure phenomena. According to observations reported by Simenauer (1927), direct stimulation of the pericardium by contact at the apex of the heart resulted in a feeling of pressure on the inner side of the left arm. Moderate pressure on the pericardium of the right ventricle was not felt, but heavier pressure resulted in an unpleasant feeling along the fourth rib.

Interference with the blood supply to the cardiac muscle, such as may be brought about by arteriosclerosis or spasm of the coronary arteries, is not infrequently accompanied by pain which is directly referable to the heart, and also by pain which is referred to the thoracic wall and along the medial aspect of one or both arms. The intensity of these pains is comparable to that of pains caused by direct stimulation of the cerebrospinal nerves. Furthermore, they are accompanied by a feeling of anxiety, vasoconstriction of the peripheral arteries, particularly in the face, and outbreaks of perspiration. The ischemic condition of the contracting cardiac muscle probably is a major factor in the production of the afferent impulses which give rise to these sensations. They are conducted centralward through the visceral afferent fibers accompanying the sympathetic nerves to the heart, but the irradiation in the thoracic

wall and upper extremities also involves somatic components of the spinal nerves through which the preganglionic and visceral afferent fibers involved in the innervation of the heart join the sympathetic trunks.

The Blood Vessels.—That pathological lesions of the blood vessels and stimulation of the vessel walls give rise to painful sensations is a fact of common clinical observation. Degenerative processes in the walls of the arteries are commonly accompanied by intense pain which tends to radiate from the site of the lesion. This pain, doubtless, is due mainly to spastic contraction of the musculature of the arteries. Constriction of the vasa vasorum, resulting in a diminished blood supply to the arterial musculature, may also be regarded as a contributing factor.

As observed by Spiegel and Wassermann (1926), pain reactions may be elicited in animals under experimental conditions by measures which bring about slight distention of the ascending aorta or the aortic arch. In their experiments, distention of a portion of the aorta, isolated by a ligature at either end, was brought about by introducing a physiological salt solution under pressure. The application of stimulating substances to the outer surface of the aorta, in their experiments, also resulted in unmistakable manifestations of pain. They were unable, however, to obtain unmistakable pain reactions in response to the injection of barium chloride, a substance which stimulates the contraction of smooth muscle, into an isolated portion of the aorta. This they attribute to the fact that the wall of the aorta is made up largely of elastic tissue and contains relatively little smooth muscle. That barium chloride injected into a peripheral artery results in intense pain has been observed by various investigators.

On the basis of their experimental results, Spiegel and Wassermann concluded that the afferent impulses which reach the central nervous system from the ascending aorta and aortic arch are conducted by the same nerves which conduct afferent impulses from the heart, viz.: the visceral afferent fibers which traverse the stellate ganglion especially on the left side. They found no evidence that the cervical sympathetic trunk plays any part in afferent conduction from the heart. While afferent conduction through the vagus nerves is not precluded, they found no evidence that the vagi play any part in the afferent conduction from the aorta of impulses which give rise to sensations of pain.

That spastic contraction of the peripheral arteries commonly gives rise to pain is generally conceded. This is well illustrated clinically in Raynaud's disease, in which exacerbations of pain coincide with the periods of maximum spasticity of the blood vessels, as indicated by the coldness of the skin and the ischemic condition of the tissues involved. Although the ischemic condition of the

tissues may be a contributing factor in the production of pain in Raynaud's disease, the fact that under experimental conditions, intense pain may be produced by measures which cause spastic contraction of the musculature of a peripheral artery, strongly suggests that arterial spasm is also the major factor in the production of pain in Raynaud's disease.

In the experiments of Fröhlich and Meyer (1922), barium chloride injected into the arteries gave rise to intense pain reactions. On the other hand, they were unable to elicit pain reactions by intravenous injection of adrenalin, a substance which also stimulates smooth muscle. This may be due to the fact that smooth muscle reacts less violently to adrenalin than to barium chloride or that, as Müller (1924) suggested, these two substances act on different components of the muscle cell.

Odermatt (1922), who made an intensive study of the sensitivity of blood vessels, regarded spasm of the vessels as comparable with intestinal colic. He was unable to demonstrate any sensitivity of the intima of the larger vessels to irritating substances. When, in his experiments, irritating substances were injected slowly into the larger arteries, pain reactions were initiated only after a latent period, but if the artery was ligated distal to the point of injection, so that the irritating substance could not flow into the capillaries, no pain reaction occurred. He concluded, therefore, that the impulses which give rise to pain, under these conditions, arise, not in the larger vessels, but in the capillaries. Odermatt also demonstrated that pain reactions may be elicited by distention of the arteries regardless of their caliber. This he regarded as due to the effect of distention of the vessels on the periarterial nerve plexus. He advanced the theory that sensitivity to substances circulating in the blood is an attribute of the capillaries and that the arteries and arterioles possess the specific function of reacting to distention of their walls. This reaction may involve local or general circulatory disturbances or painful sensations.

These conclusions are, in general, supported by clinical observations. As is well known, the intravenous injection of salvarsan and strophantin gives rise to no sensations except the pain caused by puncture of the vessel wall, unless the perivascular nerve plexus is stimulated. On the other hand, ligation and other clinical procedures affecting the arteries give rise to pain, but not all arteries are equally sensitive to insults of this kind. Ligation of the superior thyroid artery almost invariably gives rise to pain which radiates toward the mandible, but ligation of the inferior thyroid artery rarely gives rise to pain. Odermatt (1922) also observed that ligation of the common carotid, iliac, and certain of the mesenteric arteries gives rise to pain, but ligation of veins and certain arteries rarely gives rise to painful sensations. He also pointed out that

only those mesenteric arteries are sensitive to distention which also become painful on ligation. This finding strongly suggests that the pain resulting from ligation, like that resulting from distention of arteries, is due to the effect of ligation on the periarterial nerve plexus. Distention of the blood vessels, doubtless, is an important factor in the pain associated with local inflammation, *e. g.*, furunculosis. This pain not uncommonly exhibits a rhythmicity which corresponds to the pulse rhythm. It also subsides as soon as the local tension is relieved by incision or spontaneous rupture of the abscess.

Odermatt's findings have contributed materially to our knowledge of painful sensations referable to the blood vessels, and demonstrate clearly that pain of vascular origin may arise in the absence of spastic contraction of the arterial musculature. Nevertheless, arterial spasm and hypertension must still be regarded as major factors in the production of pain of vascular origin.

According to Bazett and McGlone (1928), the pain produced by arterial puncture can readily be differentiated from pain due to other causes. According to their findings, a dull aching sensation is felt when the needle reaches the arterial wall, which is less acute than the pain caused by simple puncture of the dermis, but much less bearable. It is diffuse, often referred to a more distal position, and not infrequently accompanied by uncontrollable reflex reactions. The subject may experience a sudden sensation of warmth, sweat profusely, and then feel cold, faint or actually lose consciousness. The pain accompanying puncture of different arteries is not of equal intensity. For example, that produced by puncture of the brachial is less intense than that produced by puncture of the radial artery. Puncture of small arteries beneath the deep fascia, in the experiments of Bazett and McGlone, were usually accompanied by a dull aching pain which was not easily bearable, and by reflex reactions of the fainting type. In general, in their experiments, puncture of the smaller arteries, except those in the dermis, was accompanied by more intense pain and more profound reflex reactions than puncture of the larger arteries.

The sensations accompanying venipuncture, according to Bazett and McGlone, are similar to those caused by dermal puncture alone, unless, as occasionally happens, a small nerve is affected. In the latter event, the sensations experienced are similar to those of arterial puncture, but less severe. Sensations of this type occur least rarely when a vein is punctured near a valve. The nerve supply seems to be maximal at these points.

The anatomical relationships of the fibers through which afferent impulses are conveyed from the peripheral blood vessels to the central nervous system are not fully known. Doubtless, they are components of the dorsal spinal nerve roots. Whether they occur

in all the spinal nerves or only in those which also convey pre-ganglionic visceral efferent fibers is not known. Neither is it known to what extent they traverse the sympathetic trunk. That many of them do not traverse the sympathetic trunk, but accompany the somatic afferent fibers which convey painful impulses from the periphery seems highly probable. That sensory fibers are supplied to the peripheral blood vessels in abundance is indicated by the large numbers of nerve fibers in the adventitia which cannot be traced into the deeper layers (see Chapter VII) as well as by the high degree of sensitivity exhibited by the peripheral vessels.

Alimentary Canal.—Esophagus.—The esophageal mucosa is sensitive in some degree, especially to thermal stimulation. The presence of food in the esophagus is usually not perceived unless it causes marked distention of the esophageal musculature. In tests carried out on himself, Herz (1911) was unable to discover any sensitivity of the mucous membrane of the esophagus to tactile stimulation, although the pharyngeal mucosa was found to be sensitive. In the experiments of Payne and Poulton (1927), carried out on themselves as subjects, pain localized in the portion of the esophagus involved was produced by stretching of the esophageal wall. This pain was relieved by peristaltic contractions which overcame the stretch, or by postural adaptation of the viscus which increased its capacity. Peristaltic contractions which failed to overcome the stretch resulted in more intense pain. Continuous stretching of the esophagus gave rise to burning pain (heart burn). They also experienced pain in the esophagus during muscular relaxation following a peristaltic wave. In their experiments, pain in the esophagus was always associated with high tonus and was probably caused by stretching and deformation of sensory nerve endings in the esophageal wall.

Stomach.—Many of the recorded observations regarding the sensitivity of the stomach support the theory that this viscus is insensitive to mechanical, chemical, thermal, and electrical stimuli. That it may be cut, torn, or otherwise injured during operative procedures, carried out under local anesthesia of the abdominal wall, without giving rise to pain, is a fact of surgical observation. That certain forms of gastric stimulation give rise to painful sensations, however, cannot be denied. Strong chemical stimulation of the gastric mucosa always gives rise to pain. Likewise, in certain types of gastritis, substances normal for the stomach cavity, *e. g.*, water or gastric juice, may cause pain. Strong tonus and contraction of the stomach also give rise to pain. Such reactions may also be a factor in the pain resulting from the destructive action of chemical substances on the mucosa of the normal stomach or normal stimulation of the hypersensitive mucosa. Herz (1911) advanced the theory that all so-called gastric pain is due to strong

contraction of the pylorus and pyloric portion of the stomach. According to Carlson (1916), this pain probably is essentially muscular, but the injured mucosa must also be regarded as a causative factor. Hyperdistention of the stomach causes pain which is localizable in this organ, but there is no evidence that the nerves supplying the mucosa play any part in such pain. According to Carlson, the only pains arising from the stomach under normal physiological conditions are the pangs of hunger, in which the innervation of the mucosa plays no part. Probably all pain due to impulses arising in the gastric mucosa may be regarded as an index of pathological processes, *i. e.*, either normal stimuli acting on the hypersensitive mucosa or destructive stimuli acting on the normal mucosa.

That the normal gastric mucosa is devoid of tactile sensibility is quite generally conceded. Its sensitivity to thermal stimulation has been studied extensively. The majority of the recorded observations indicate that hot or cold substances introduced into the stomach give rise to vague hot or cold sensations in the region of the epigastrium, but not all the investigators were convinced that the sensations arise in the gastric mucosa. For example, Weber (1846) assumed that sufficient conduction takes place through the walls of the stomach and abdomen to stimulate the temperature receptors in the skin. Mackenzie explained the temperature sensations resulting from the introduction of hot and cold water into the stomach on the basis of reflex vasomotor changes in the skin of the abdomen. Herz advanced the opinion that temperature sensations felt in the epigastrium upon drinking hot or cold water come from the lower end of the esophagus.

In experiments carried out on themselves, Neumann (1906) and Roux (1907) experienced temperature sensations in the stomach when hot or cold water was introduced into it through a double rubber tube. In Boring's (1915) experiments, water at 30° C. produced a sensation of cold and water at 40° C. a sensation of warmth in the stomach. On the basis of his findings, he concluded that these sensations arise either in the stomach or in some tissue nearer to it than the esophagus or abdominal wall. On the basis of the results of an extensive series of experiments carried out on himself and other persons, Carlson (1916) advanced the following conclusions: "(1) The stomach mucosa is endowed with heat and cold nerve endings. (2) These fibers are, as Head suggests, of the protopathic type; that is, they are not stimulated by slight temperature changes, or if they are, the impulses do not affect consciousness. (3) They are more abundant, or more readily stimulated in the throat and esophagus than in the stomach."

Regarding the sensitivity of the gastric mucosa to chemical stimulation, it may be stated that substances like pepper, mustard,

strong alcohol, or acid (5 to 20 per cent HCl), etc., introduced into the stomach through a tube in sufficient quantity give rise to varying degrees of pain, accompanied at first by a sensation of warmth in the stomach (Carlson, 1916). All chemicals taken into the stomach in sufficient concentration to cause pain, however, probably injure the mucosa and the nerve endings in it, as is indicated by the development of gastritis. When chemical substances are taken into the stomach in dilutions which do not cause pain or discomfort, their contact with the mucosa may still give rise to sensations which are not akin to pain, but resemble appetite. In Carlson's experiments, the sensations produced by such substances as beer, wine, weak acid (0.5 to 2 per cent HCl), weak alcohol, or carbonated drinks, introduced into the stomach through a tube, were rather transitory, but characteristic, and could not always be distinguished from appetite. That this sensation is due to stimulation of the nerve endings in the gastric mucosa, is indicated by the fact that it arises immediately when the appropriate substances are introduced into the stomach, even though this organ be quiescent and very greatly relaxed. It is not dependent on gastric motility. Furthermore, it differs qualitatively from the sensation of relief following relaxation of the stomach at the end of a period of hunger contractions, in that it has the positive character that directs attention to food and eating. When the gastric mucosa is stimulated in this manner during a period of hunger contractions it is quite impossible to differentiate the sensation caused by the chemical stimulus from the sensation of relief from hunger. On the basis of these experimental findings, it is evident that chemical stimulation of the gastric mucosa plays an important rôle in appetite and the desire for food.

On the basis of extensive experimental observations and a review of the literature bearing on the subject, Herz (1911) concluded that "the sensation of fulness in the stomach is due to tension on its muscular coat, and depends very little, and only in extreme cases, on the stretching of the abdominal wall." Impulses arising in the gastric mucosa probably play no part in the sensations of fulness. As pointed out by Carlson (1916), tension on the gastric musculature alone, *i. e.*, intragastric pressure, does not, under all conditions, result in a sensation of fulness. He was able to show that the intragastric pressure at the height of a period of hunger contractions of the empty stomach, when distended by a rubber balloon frequently exceeds that which, according to Herz, is required to cause a sensation of fulness, yet the sensation experienced under these conditions is not one of fulness, but of emptiness. He concluded, therefore, "that a certain amount of tonus reaction of the stomach must be present before tension or pressure on the walls of the stomach produce the sensation of fulness."

The sensation of satiety following a palatable meal probably arises independently of impulses emanating from the gastric mucosa. In order to insure this sensation, eating must be preceded by some degree of hunger and appetite, the food must be palatable and must be eaten in sufficient quantity to produce moderate distention of the stomach but not the sensation of fullness. The sensation of satiety, according to Carlson, "involves the element of contrast between the uncomfortable tension of hunger and the sensation of fullness, together with the lingering memories of the taste and smell of the food."

Nausea is a very complex sensation which is referable only in part to the stomach. It may be initiated by stimulation of the gastric mucosa, but usually involves other factors, and not infrequently arises entirely independently of gastric disorder. Yet, it probably always involves a characteristic feeling of distress referable to the stomach. Under certain conditions, nausea seems to be allied to hunger. In Boring's experiments, some of the subjects (normal men) confused mild nausea with hunger. Such confusion of nausea with hunger is regarded by Carlson either as pathological or due to superficial analysis. Both nausea and hunger involve sensations of uncomfortable tension and pain, and cause salivation. In some persons, both these states also involve bodily weakness, headache, dizziness, etc., but "the distinct 'sickness' character of the gastric distress in nausea," according to Carlson, is lacking in normal persons in any stage of hunger. In normal persons, the central effects by nausea are also unlike those produced by hunger. Nausea is incompatible with appetite, but hunger commonly intensifies the desire for food. Since hunger, though normally caused by stimulation of the kinesthetic nerves of the stomach may, like nausea, be caused by stimulation of the nerves of the gastric mucosa, it is not unlikely that, in persons with an unstable central nervous organization, intense hunger may be accompanied by nausea, or become apparently identical with it.

In the early discussions of hunger and its genesis, the sensations of appetite and hunger were not clearly differentiated. It is now known that the gastric factor in appetite depends mainly on moderate chemical stimulation of the nerves of the gastric mucosa, while the sensation of hunger arises from stimulation of nerves in the submucosa or muscularis by a certain type of contraction of the empty or nearly empty stomach, which has been called the hunger contraction (Carlson, 1916). Certain investigators had previously pointed out that the stomachs in starving men and animals are tonically contracted, but the first systematic study of gastric motility during starvation was carried out by Boldireff (1905). He observed that in dogs, at least during the first three to four days of starvation, the stomach exhibits alternate periods of strong con-

tractions and absolute quiescence. In his experiments, the periods of contraction lasted twenty to thirty minutes, the periods of quiescence one and a half to two and a half hours. During a period of activity 10 to 20 contractions separated by intervals of one to one and a half minutes took place. The contractions were at first feeble and gradually reached their maximum strength at the end of the period. Contractions of the intestine were also observed during these periods. Boldireff observed that these contractions of the empty stomach are stronger than gastric peristalsis during digestion, but he did not associate them with the cause of the sensation of hunger, mainly because he observed that they diminish in strength with the length of the period of starvation. He advanced the opinion that the contractions of the stomach and intestine during starvation are initiated through the vagi by the state of hunger in the brain.

In a series of experiments carried out on a man, in which a graphic record of the gastric contractions was obtained by means of a rubber balloon which had been swallowed into the stomach, Cannon and Washburn (1911) were able to show that the periods of contractions of the empty stomach coincide with the periods of hunger sensation, and that each contraction synchronizes with a hunger pang. They also obtained evidence that contractions occur in the lower third of the esophagus which are synchronous with the gastric contractions; therefore, they concluded that the contractions of the esophagus also play a part in hunger. Furthermore, they noted that the sensation of hunger tends to lag behind the gastric contraction both at its beginning and its termination. On the basis of their experimental results, they concluded that these contractions of the stomach and lower third of the esophagus cause the sensation of hunger through stimulation of sensory nerves, but they did not state whether the nerves in question are those which supply the gastric mucosa or the muscularis.

Although the assumption of Cannon and Washburn was essentially correct, it remained for Carlson and his students (1912) to demonstrate, in man and experimental animals, that the sensation of hunger is caused by a certain type of contractions of the empty or nearly empty stomach, and that the sensory nerve fibers involved are not those which supply the gastric mucosa, but those which supply the submucosa or muscularis. Carlson (1914) also obtained certain experimental evidence which he interpreted as indicating that the hunger contractions are initiated in the stomach itself and are, in a large measure, independent of efferent impulses emanating from the central nervous system. In his experiments, moderate exercise had little stimulating effect on gastric tonus and hunger contractions. Moderate stimulation of the nerve endings for cold had no effect, but intense stimulation of these nerve endings inhib-

ited hunger contractions. As an after-effect there was an increase in gastric tonus and hunger contractions. Intellectual processes seemed to have no effect except as they caused inhibition of gastric tonus and hunger contractions through the splanchnic nerves. On the basis of these experimental findings, he concluded that "in normal individuals (man, dog) the vagogastric tonus apparatus, at least so far as it concerns the empty stomach, is physiologically isolated from the exteroceptors and from many, if not all, central processes." He admitted, however, that this mechanism is affected by the nutrient content of the blood when he advanced the opinion that "the biological significance of this exceptional and unique isolation of the tonus apparatus of the hunger mechanism probably lies in the importance of the hunger mechanism being regulated on its positive side primarily by the state of nutrition, that is, through the blood rather than by the fleeting changes in the nervous system."

That depletion of the nutrient substances in the circulating blood is an important factor in the production of hunger is obvious. Emptiness of the stomach alone is not sufficient to cause hunger; the stomach may be empty for several hours before the sensation of hunger arises. Furthermore, the sensation of hunger subsides temporarily following the subcutaneous injection of a nutrient solution, *e. g.*, glucose, even though the stomach remains empty (Thoma, 1915). It has also been observed clinically that, under certain pathological conditions, the stomach may remain empty for days without giving rise to hunger sensations. On the other hand, a patient with pyloric stenosis may experience intense hunger, although the stomach is filled with food.

Although moderate physical exercise, as pointed out by Carlson, has little immediate effect on the hunger contractions of the stomach, it is well known that vigorous physical exercise hastens the onset of hunger. This points very definitely to the nutritive content of the blood as a factor in the sensation of hunger. Thoma (1915) advanced the opinion that a certain center in the brain reacts to the lack of nutrient material in the blood by sending out efferent impulses which bring about reactions, which in turn initiate afferent impulses resulting in the sensation of hunger, just as the respiratory center reacts to the lack of oxygen in the blood by sending out efferent impulses which accelerate the respiratory movements. He also advanced the opinion that the center in question is closely associated with the temperature-regulating center. This he believes is indicated by the fact that hunger not uncommonly subsides during fever. Furthermore, he observed that animals in which the so-called temperature puncture in the diencephalon was successfully carried out lost their desire for food. Although unable to localize the center in question more definitely, he assumed that an aggregate of nerve cells exists in the brain stem which reacts to the

lack of nutrient material in the blood by giving rise to efferent impulses, and that these impulses are conveyed peripherally through the vagus nerves and call forth contractions of the empty stomach as well as secretory activity of the gastric glands. The contractions of the stomach in turn give rise to afferent impulses which result in sensations referable to that organ.

Although the stomach may be cut, torn, or otherwise injured without giving rise to pain, impulses arising in the stomach, under certain pathological conditions, give rise to painful sensations which are directly referable to this organ. The same impulses may also give rise to sensations which are referable to the body wall.

The data available at present strongly suggest that the chief causes of gastric pain are hyperdistention of the stomach wall and spastic contractions of the gastric musculature. That gastric ulcer involving only the gastric mucosa may be the underlying cause of gastric pain is generally conceded. On the other hand, gastric ulceration may, in some cases, go on to the point of perforation without giving rise to pain. It seems highly improbable, therefore, that the pain which, in many cases, is associated with gastric ulcer is mediated through the nerves supplying the gastric mucosa. Not uncommonly the onset of this pain bears a definite relationship to the time of eating. It does not occur immediately following the ingestion of food, but after the food has become thoroughly mixed with gastric juice and is ready to be discharged into the duodenum. As has been shown by fluoroscopic examination of patients with gastric ulcer, the pain, in many instances, coincides with a period of peristaltic contractions which sweep over the pyloric portion of the stomach against the contracted pylorus. These contractions of the *pars pylorica* probably constitute the major factor in the genesis of gastric pain under these conditions. According to Carlson (1918), they are usually not stronger than the normal peristaltic contractions of the filled stomach or the hunger contractions of the empty stomach. A condition of hyperexcitability of the gastric pain nerves is, therefore, indicated in ulcer patients who experience the typical ulcer pains.

Certain patients with gastric ulcer also experience pain while the stomach is empty. It has been assumed by certain investigators that the contractions which give rise to the pain in such cases are caused by gastric hyperacidity. As pointed out by Carlson, the motility of the stomach is in a large measure independent of the chemical reaction of the stomach contents; however, high gastric acidity intensifies and prolongs the duodenal reflex contractions of the pylorus and also induces strong duodenal contractions. These pains are commonly alleviated by the ingestion of substances (protein food, water, alkalies) which temporarily lower gastric acidity, provided there is sufficient relaxation of the pylorus to permit the

gastric content to pass into the duodenum. Ulcer pains which are due to tonus or contractions of the body of the stomach are commonly alleviated temporarily by any measure which inhibits or decreases gastric tonus, irrespective of the chemical reaction of the stomach contents. The continuous pain in the epigastric region, which is present in certain cases of gastric ulcer, is probably due to persistent exaggerated tonus of the stomach or pylorus. The more severe exacerbations of this pain are probably due to pyloric spasm (Carlson, 1918).

Palmer (1927) was able to elicit pain, in cases of gastric ulcer, when the acidity of the stomach contents was normal. In general, he found little connection between the pain and gastric tonus or motility, although he conceded that gastric hyperperistalsis may be a contributing factor in some cases. Strauss (1928), who had previously maintained that free hydrochloric acid in the stomach and a zone of inflammation around the eroded area are important factors in the production of ulcer pains, was convinced, by the results of his later studies, that an excessive amount of normal gastric juice may stimulate the nerves through which the pain of gastric ulcer is mediated. He also conceded that gastric peristalsis may play a contributing rôle.

On the basis of extensive clinical and experimental studies, Balint (1928) advanced the conclusion that the pain of gastric ulcer is not caused by gastric hyperacidity, but that it is produced by two factors acting simultaneously, viz.: contraction of the gastric musculature and a shift in the hydrogen-ion concentration of the blood toward the acid side. He called attention to the fact, recorded by various investigators, that the introduction of acid in relatively high concentration into the stomach of a gastric ulcer patient does not elicit pain. In his own clinical experiments, the gastric ulcer pains subsided following the contemplation and mastication of palatable food by the patient, although none of it was swallowed. The effect on the ulcer pain of such sham feeding was similar to that of the introduction of food into the stomach, although the acidity of the gastric contents was appreciably increased by reason of the increased activity of the gastric glands due to the stimulus afforded by the sham feeding. Balint also maintained that the alleviation of ulcer pain by alkali therapy does not depend on neutralization of the acid in the stomach since such therapy not infrequently results in the alleviation of ulcer pains in cases which exhibit anacidity as well as in cases which still exhibit gastric hyperacidity following alkali treatment. He also pointed out that the intravenous injection of alkali produces the same result. This supports the conclusion that the therapeutic effect of alkali, in cases of gastric ulcer, depends mainly on its effect on the hydrogen-ion concentration of the blood. This conclusion is also supported by the

fact that ulcer pains are alleviated by hyperventilation of the lungs, which has the same effect on the acid-base balance of the blood as alkali therapy. That changes in the acid-base balance of the blood toward the acid side play a rôle in the causation of ulcer pains is also suggested by the fact that other therapeutic agents which tend to shift the acid-base balance toward the basic side, *e. g.*, atropin, Roentgen radiation, etc., also tend to alleviate these pains, whereas, measures which tend to shift the acid-base balance of the blood toward the acid side, *e. g.*, physical exertion, aggravate the ulcer pains. Inasmuch as gastric ulcer pains commonly accompany gastric motility, and this motility must be regarded as a factor in their causation, it may be assumed that the influence of changes in the acid-base reaction of the blood in the causation of ulcer pains is due, at least in part, to the effect of these changes on the functional balance between the sympathetic and parasympathetic components of the autonomic system, which is, in turn, reflected in the gastric motility.

The pain experienced in cases of acute gastritis is also due to impulses arising in the deeper layers of the stomach wall. The symptom complex, in these cases, affords no evidence that impulses arising in the inflamed gastric mucosa play any direct part in the production of pain. Pain arises, in these cases, only when the stomach becomes distended by reason of faulty emptying or generation of gas, and probably is due to hyperdistention of the stomach wall or contraction of the gastric musculature. The normal stomach may react in essentially the same manner when overfilled with food of low digestibility. Under these conditions the subject may experience discomfort due to pressure, or even acute pain. The efferent impulses involved arise, not in the gastric mucosa, but in the deeper layers of the stomach wall.

All the data available regarding the conduction of afferent impulses from the stomach indicate quite clearly that those impulses which give rise to pain are conducted solely by the splanchnic nerves. The vagi conduct afferent impulses from the stomach, which bring about various reflex reactions which affect consciousness, but impulses of gastric origin conveyed by the vagi do not reach the threshold of consciousness.

Intestine.—Like the stomach, the intestine is, in general, insensitive to the ordinary stimuli. Appropriate stimulation of the intestine, however, gives rise to impulses which result in pain of varying degrees of intensity. Not infrequently, strong contractions of the intestine give rise to pain which is more or less definitely localizable in the abdomen. Limitation of the blood supply to the intestine, such as occurs in cases of advanced arteriosclerosis of the aorta constricting the portals of the mesenteric arteries, also gives rise to intense intestinal pain, particularly while digestive activity is at

its height (Müller, 1924). On the other hand, ulceration of the intestine, such as occurs in typhoid and tuberculosis, may exist without giving rise to any sensations. Such lesions of the intestine may, however, through stimulation of the enteric plexuses, bring about hypermotility of the intestine which, under certain conditions, results in pain. Likewise, the powerful contractions of the intestinal musculature which occur in cases of partial or complete intestinal occlusion, resulting from carcinoma or other causes, also give rise to pain of varying degrees of intensity.

Various hypotheses have been advanced to explain the cause of pain in duodenal ulcer. This pain has been ascribed to irritation of the exposed nerve endings in the ulcerated area by the acid gastric juice (Gonninger, 1908; Palmer, 1927; and others), mechanical irritation by coarse particles of food (Pick, 1913), spasm of the pyloric sphincter or duodenal cap (Glaessner and Kreuzfuchs, 1913), tension due to inhibition of relaxation of the pyloric sphincter, combined with strong gastric peristalsis (Hurst, 1921), and various other causes. In a recent clinical study, Wilson (1928) found no direct relationship between the acidity of the gastric contents and the occurrence of pain in patients with duodenal ulcer, although the common experience of relief from the pain of duodenal ulcer by the administration of alkalis strongly suggests that gastric hyperacidity may be a factor in the production of pain. Neither did he find a direct relationship between the occurrence of pain in duodenal ulcer and gastric motility or the tonic state of the pyloric sphincter. In his experience, the pain of duodenal ulcer was nearly always relieved by squeezing gastric contents into the duodenal caput, regardless of the gastric acidity. In those cases in which the pain was not relieved by this procedure, it was apparent that the musculature of the duodenal caput was not relaxed. On the basis of his findings, he advanced the hypothesis that the pain of duodenal ulcer is due to sustained contraction of the duodenal caput.

On the basis of the results of animal experimentation, Breslauer advanced the theory that the impulses which initiate the so-called intestinal pain do not arise in the intestine, but in the mesenteric blood vessels. He was unable to elicit pain reactions in his experimental animals by distention or stretching of parts of the intestine, but such reactions were always elicited by traction on the mesentery. He also observed that areas of the peritoneum which contain large blood vessels are more sensitive than areas in which no large vessels are present. He concluded, therefore, that pain caused by traction on the mesentery is due mainly to stretching of the larger mesenteric vessels. That traction on the mesentery gives rise to pain is a fact of common clinical experience. Furthermore, traction on the mesentery and irritation of the parietal peritoneum must be regarded as factors in the genesis of many abdominal pains. The pain asso-

ciated with certain intestinal disturbances, *e. g.*, intestinal colic and luetic crises, cannot be accounted for on this basis, since there is no evidence that traction is exerted on the mesentery in these conditions. Neither can it be accounted for on the basis of pressure exerted on the parietal peritoneum, since it is not evident that the spastic intestine exerts any unusual pressure against the abdominal wall. The pains arising in these conditions can best be explained as the result of afferent impulses initiated in the intestinal wall by the contraction of its musculature.

All the available evidence indicates that the conduction from the intestine of afferent impulses which give rise to pain is accomplished through the splanchnic nerves. On the basis of his own experience as a patient following two abdominal operations (cholecystectomy and appendectomy) and during three attacks of acute gastroenteritis, Brüning (1921) advanced the theory that pure intestinal pain is not localized in the portion of the intestine in which the afferent impulses arise, but at the site of the abdominal sympathetic ganglia through which this portion of the intestine is innervated; consequently, pain due to impulses arising in the small intestine is felt at the site of the coeliac ganglia, while pain due to impulses arising in the portion of the large intestine which is innervated through the inferior mesenteric plexus is felt at the site of the inferior mesenteric ganglia. He further expressed the opinion that the afferent impulses involved in intestinal pain are conducted to these sympathetic ganglia by sympathetic fibers and are there transferred to cerebrospinal fibers through which they reach the spinal cord.

This opinion of Brüning regarding afferent conduction from the visceral organs is at variance with the current teaching. That the visceral afferent components of the splanchnic nerves which supply the intestine traverse the coeliac ganglia and reach the intestine through the mesenteric nerves is well known. Although Brüning's interpretation of his own experiences regarding the localization of intestinal pain cannot be questioned, it need not be assumed that the conduction from any part of the intestine of afferent impulses which give rise to pain involves any fibers other than visceral efferent components of the spinal nerves.

That the terminal portion of the large intestine, *viz.*: the pelvic colon and rectum, are sensitive in a certain degree to stimuli other than those which give rise to pain is well known. This is also in keeping with the functional requirements of the lower portion of the digestive tube. Zimmerman was able to show, by the use of a manometer, that pressure in the rectum equal to 20 mm. of mercury may give rise to a distinct sensation of pressure. Even differences in pressure of only 2 or 3 mm. of mercury could be clearly perceived. This sensitivity of the terminal portion of the digestive tube must

be regarded as an important factor in its functional regulation. It also illustrates the general principle that receptors for various types of stimuli exist in all parts of the body in which they are demanded by the vital interests of the organism.

Liver and Biliary System.—The parenchyma of the liver may be regarded as insensitive to the ordinary stimuli. It may be cut, torn, or otherwise injured without giving rise to any sensations. Neither do inflammatory processes and ulceration in the liver give rise to impulses which reach the threshold of consciousness. The serous covering of the liver is also anesthetic. Inflammatory processes which involve the parietal peritoneum give rise to painful sensations, but they are not directly referable to the liver. Rapid enlargement of the liver, such as occurs in cases of cardiac decompensation, not infrequently gives rise to pain and sensations of pressure in the epigastric region. Although the cause of these sensations is not definitely known, it may be assumed that distention of the hepatic capsule and the weight of the enlarged organ pulling downward on its attachments to the diaphragm constitute important contributing factors.

In general, the gall bladder and bile ducts may also be regarded as anesthetic to the ordinary stimuli. The pain experienced in attacks of biliary colic and other disturbances of the biliary system, like pain arising in other visceral organs containing smooth muscle, probably is due to impulses arising from hyperdistention or spastic contraction of the musculature of the bile ducts. In a recent experimental investigation carried out on dogs, Gubergritz, Itschenko, and Goldstein (1926) were able to elicit pain reactions by distention of parts of the biliary system with warm water, introduced into the common bile duct through a cannula inserted through its opening into the intestine. On the basis of their experimental results, they concluded that both spasm and distention of the biliary musculature may give rise to pain. A certain degree of distention seemed to be necessary to produce pain, and the pain became more intense as the distention was increased by introducing more water. Yet, distention was not the only factor involved. It seemed probable that distention of the bile ducts with water caused spastic contraction of their smooth musculature, and that this in turn increased the pain. Distention of the bile ducts alone may give rise to slight pain, but spastic contraction of the biliary musculature probably constitutes the major factor in the genesis of biliary pain. These experimental findings are in full accord with clinical observations. The dull pain associated with biliary stasis is probably due mainly to distention of the biliary musculature, but the acute pain of biliary colic is due to spastic contraction of this musculature.

Gubergritz, Itschenko, and Goldstein were also able to show that the afferent impulses involved in biliary pain are conducted by fibers

which traverse the hepatic portal and reach the spinal cord through the splanchnic nerves. No pain reactions could be elicited by experimental distention of the bile ducts in animals which had previously been subjected to denervation of the liver by cutting all the nerves in the portal canal and hepato-gastric ligament. The vagus fibers supplying the liver play no part in the afferent conduction of impulses which give rise to pain.

Pancreas.—The pancreas may be regarded as insensitive to the ordinary stimuli, yet certain pancreatic lesions are known to give rise to excruciating pain. The clinical manifestations, in these cases, are so complex that it is quite impossible to determine the exact sources of the afferent impulses involved. There is no clear evidence that these impulses arise solely in the pancreas. They may arise in part in the blood vessels through which the pancreas is supplied. If, by reason of a pancreatic lesion, autodigestion takes place, this may involve not only the large abdominal sympathetic plexuses, but also components of the spinal nerves.

Spleen.—The spleen may also be regarded as insensitive to the ordinary stimuli. Neither is it known that impulses arising in this organ ever reach the threshold of consciousness. That inflammation of the serosa of the spleen may give rise to pain is well known; but this probably is due to involvement of the parietal peritoneum. The pain associated with enlargement of the spleen probably is due to traction on the splenic attachments.

Kidneys—The kidneys, like other visceral organs, may be cut, torn or otherwise injured without causing any sensations. The renal pelvis, however, seems to be sensitive under certain conditions. Although mere contact results in no sensations, contact of this part of the organ with hot or cold objects gives rise to pain (Gubergitz and Itschenko, 1926). According to Müller (1924), pain sensibility seems to be a peculiar property of the renal pelvis. Renal pain probably arises in this part of the organ in the majority of cases. Traction on the kidney also gives rise to pain. Doubtless, this is due in large measure to the pull on the renal blood vessels and parietal peritoneum. Kappis expressed the opinion that renal pain can be explained most satisfactorily on the basis of stimulation of the sensory fiber terminations in the prerenal peritoneum, particularly at the level of the root of the kidney. Renal pain is commonly localized in the back just below the costal margin, and not uncommonly radiates to the ovary or testis and along the ureter to the bladder. In some cases, it also radiates into the thigh.

Pathological conditions of the kidney are commonly accompanied by pain. In a limited number of cases, the pain is due at least in part to traction caused by shifting of the position of the organ. In cases of renal enlargement, the sensory nerves in the adjacent parietal peritoneum may be stimulated by pressure. Many authors

have regarded this as one of the major factors in renal pain. Distention of the renal capsule has also been regarded as a factor in producing painful stimulation. It is well known, however, that a shrunken kidney may also give rise to pain, although its capsule is not under tension.

Gubergritz and Itschenko (1926) were able to show, in experimental animals, that ureteral catheterization does not necessarily give rise to pain. In their experiments, distention of the renal pelvis by the introduction of water through the ureteral catheter commonly elicited pain reactions, except when the renal plexus had previously been divided. They regarded distention of the renal capsule only as a secondary factor in the production of renal pain. Inasmuch as pain reactions could not be elicited by distention of the renal pelvis following denervation of the kidney by section of the nerves along the renal vessels, they concluded that the afferent impulses involved are conducted through the renal plexus and reach the spinal cord via the splanchnic nerves. Although pain of renal origin may, under certain conditions, involve conduction through somatic afferent fibers supplying the adjacent parietal peritoneum, it may in general be assumed that impulses which give rise to renal pain are mediated through the visceral afferent fibers which traverse the renal plexus.

Urinary Bladder.—That the urinary bladder is sensitive to certain types of stimulation is generally conceded. Under normal conditions, the urge to micturate depends on afferent impulses which arise in the bladder; consequently, sensations which have their origin in the urinary bladder play an important rôle in the functional regulation of this viscus. Overdistention of the bladder not only results in a strong desire to micturate, but also gives rise to acute pain.

The mucosa of the bladder, like that of the gastro-intestinal canal, is insensitive to the ordinary stimuli. Contact of the bladder mucosa with a metallic catheter gives rise to no sensation, although the catheter is felt at the sphincter vesicæ. Contact of the catheter at the openings of the ureters into the bladder is felt in some cases. This probably is due to anatomical variations in the distribution of sensory nerves. Neither is the bladder mucosa sensitive to changes in temperature. Irrigation of the bladder with hot or cold water gives rise to no temperature sensations. The pain caused by electrical stimulation of the bladder mucosa probably is due to contraction of the bladder musculature. Likewise, the pain resulting from cystitis and ulceration of the bladder mucosa is not due to the direct effect of the lesion of the mucosa, but to reflex muscle spasm.

Under normal conditions, the urge to micturate arises only after some degree of distention of the bladder wall, but distention of the

bladder musculature probably is not the cause of the sensation. If it were, the urge to micturate would be continuous and become progressively stronger as the bladder becomes more and more distended by the increasing volume of its contents. Such, however, is not the case. According to Schwartz (1920), the sensations which give rise to the urge to micturate have their cause in the contraction of the detrusor muscle. On the other hand, Adler (1920) advanced the opinion that these sensations are caused by contractions of the internal sphincter vesicæ. Both these processes probably play a part in the production of vesical sensations. Müller (1924) expressed the opinion that the indefinite sensations felt in the region of the bladder, but which are not definitely localizable, are caused by contraction of the bladder musculature, while the more acute sensations which are more or less definitely localizable at the neck of the bladder are caused by contraction of the musculature in that region.

Although afferent impulses arising in the bladder may reach the central nervous system via the hypogastric nerves, the afferent conduction of impulses which give rise to vesical sensations is mediated mainly through the pelvic nerves. According to Fröhlich and Meyer (1922), the sensitivity of the bladder is not affected by section of the hypogastric nerves. They were unable to elicit any reactions in experimental animals by electrical stimulation of the bladder following section of the dorsal roots of the sacral nerves, although the hypogastric nerves remained intact. Impulses arising in the sphincters of the bladder reach the central nervous system via the pudendal nerve.

Female Genitalia.—The vaginal mucosa, like the mucosa of the other hollow viscera, may be regarded as insensitive to the ordinary stimuli. Neither do these stimuli when applied to the uterus, Fallopian tubes, or ovaries give rise to sensations unless they cause traction on the parietal peritoneum or the attachments of the organs in question to the body wall. Pains arising in the uterus are due mainly to contractions of the uterine musculature. Pains resulting from displacement of the uterus are not directly referable to this organ. They probably are due mainly to the effect of its displacement on adjacent structures.

REFERRED PAIN.

Nature and Localization of Referred Sensations.—Analysis of the data bearing on the causes of visceral sensations shows clearly that the adequate stimulus perhaps always involves contraction or hypertension of the smooth musculature of the viscus itself or the blood vessels through which it is supplied. The visceral sense may, therefore, be regarded as smooth muscle sense. Sensations of fulness

or emptiness of a hollow viscus, *e. g.*, the stomach, are comparable to sensations of posture in skeletal muscles. Just as hypertension or spastic contraction of skeletal muscles give rise to somatic pain, hypertension or exaggerated contraction of smooth muscle gives rise to visceral pain. Under certain conditions, visceral pain is localized not only in the viscus which is the site of its origin, but also in a somatic area which is supplied by nerves connected with the same segments of the central nervous system as those which supply the viscus in question. Pain which is localized in an area other than that which is the site of its origin is known as referred pain. As shown by the early studies of Head, the somatic areas in which referred pains are localized always fall within the segments which are supplied by those spinal nerves through which the viscus in question is also supplied. Not infrequently visceral lesions give rise, not to sensations which are distinctly painful, but to hyperalgesia or tenderness in the corresponding somatic area. Such hyperalgesia may exist even in the absence of deep visceral pain.

Nature of Visceral Lesions Which Are Commonly Accompanied by Referred Pain.—According to Ryle (1926), non-inflammatory visceral lesions rarely give rise to referred pain or somatic hyperalgesia unless they fall into the group of severe visceral crises. He regards referred pain as less prevalent in visceral disease than current clinical conceptions seem to indicate. While the statements of patients regarding their own subjective symptoms cannot always be relied upon, he regards certain gestures of the patient as important. These gestures do not, as a rule, apply to the somatic segment, but to the area occupied by the visceral organs in question. In the case of anginal pain, the patient not uncommonly places the clenched hand on the sternum, as though to indicate that the pain has its origin in the aorta. Incidentally the clenching of the hand may imply the gripping character of the pain. Cardiac pain is commonly indicated by the flat hand in the left submammary area. The location of the pain in case of gastric ulcer is not infrequently indicated by placing two or three fingers in the mid-epigastric region or a little to the left of this. The pain of duodenal ulcer is usually localized at the right of the mid-line. In the case of renal colic, the patient grasps the back with the fingers toward the spine in the region of the kidney, indicating deep pain in the position of this organ. The pain associated with appendicitis and gall-bladder disease is usually localized with remarkable accuracy unless inflammation or other gastro-intestinal lesions are associated with it. Likewise, the position of a calculus in the ureter can be localized quite accurately unless there is associated renal pain. Intestinal pain is usually localized less accurately. This is due, at least in part, to the changing position of the painful contractions. Pain arising in the small intestine is not infrequently localized in the

region around the umbilicus; pain arising in the large intestine is usually localized between the umbilicus and symphysis pubis. Obstruction of the intestine at a fixed point, *e. g.*, the hepatic flexure, is usually localized with remarkable precision.

Referred pain is best demonstrated (1) in cases of severe visceral pain, and (2) in association with inflammatory visceral disease. The pain which radiates into the arm in cases of angina pectoris, the subscapular pain of cholelithiasis, and the testicular pain of ureteral colic are classical examples of the first group. Cutaneous hyperalgesia and muscular rigidity in the corresponding areas of the abdominal wall in cases of appendicitis and chronic gastric ulcer are classical examples of the second. It is worthy of note that these phenomena are associated mainly with diseases which involve organic changes in the viscus in question, but rarely accompany diseases of a functional type. For example, cutaneous hyperalgesia and muscular guarding are rarely, if ever, associated with gastric pain due to extragastric causes. The subscapular pain of cholelithiasis may be due to cholecystitis as well as the presence of gall stones. That it may occur in cases of cholecystitis, in the absence of gall stones, is well known. Furthermore, in the presence of gall stones, inflammation of the gall bladder can hardly be ruled out as a contributing factor in the referred pain. Testicular pain, according to Ryle, does not occur in ureteral colic unless the ureteral mucosa is inflamed or ulcerated. It may also occur in association with ureteral lesions in the absence of ureteral colic. On the basis of extensive clinical observations, Ryle concluded that "visceral pain expresses a perturbation of visceral function (which may or may not be due to local organic disease) while the somatic phenomena generally express a structural lesion of the wall of the viscus."

In many cases of visceral disease, the somatic manifestations are not coincident with the visceral pain. Furthermore, they may persist for some time after the visceral pain has subsided. Gastric ulcer is not uncommonly accompanied by tenderness, less commonly by superficial and deep hyperalgesia in the epigastric region, together with rigidity of one or the other rectus muscles and exaggerated abdominal reflexes on one side. These signs are most apt to be present if the patient has had a recent attack or is in pain at the time of the examination, but in many cases, they persist for days after the visceral pain has subsided by reason of appropriate treatment. They cannot, therefore, be directly attributed to the gastric contractions which are the cause of the gastric pain, although they may be reinforced by these contractions. More probably they are due to a more or less constant flow of impulses from the site of the gastric lesion to the spinal cord, from whence irradiation takes place along the nerves supplying the somatic segments in question. The somatic manifestations of gastric ulcer are more constant when the

ulcer invades the muscle layers than when it involves only the mucosa. On the other hand, gastric carcinoma is rarely accompanied by somatic hyperalgesia or referred pain. This discrepancy probably is due to the fact that simple ulcer erodes the tissue and directly affects the sensory nerve endings in the muscles, while carcinoma invades the muscle by growing between the muscle fibers. Simple gastritis is rarely accompanied by somatic signs, probably because the lesion is too superficial to affect the nerve endings in the muscle (Ryle, 1926).

The pain of biliary colic is commonly localized in the region of the gall bladder. Not infrequently this pain cannot be clearly dissociated from the attendant gastric pain. The referred manifestations of cholecystitis, whether occurring with or without gall stones, include superficial and deep tenderness in the right upper quadrant of the abdomen, pain in the right subscapular and interscapular regions, and tenderness over the middle dorsal spines and along the eleventh right rib. Muscular rigidity may also be present in the right upper abdominal quadrant in acute cases, and exaggeration of the abdominal reflex on the right side in subacute cases. The shoulder pain, commonly referred to as a sign of cholelithiasis, probably occurs only in cases in which the inflammation involves the under surface of the diaphragm, thus affecting the phrenic nerve directly, and in cases of diaphragmatic pleurisy.

The varieties of disease commonly regarded as acute appendicitis include two broad clinical types, viz.: the inflammatory and the gangrenous. In the inflammatory type, cutaneous hyperalgesia and muscular guarding or rigidity are commonly present in addition to visceral pain. These reflex manifestations are sometimes present in the mildest and earliest cases, where they constitute an important diagnostic sign. In the gangrenous type, the onset of the disease may be marked by severe visceral pain, but not infrequently cutaneous hyperalgesia and muscular rigidity are entirely absent. Possibly the absence of somatic manifestations in these cases may be explained by the mechanical nature of the lesion in the early stages, and restriction of the blood supply to the tissues involved in the later stages. In the gangrenous appendix the circulation as well as the lumen is obstructed. The fact that the visceral pain subsides suddenly in either type of the disease when the appendix ruptures strongly supports the theory that the visceral pain is caused by hypertension. The referred pain is commonly localized in the area of the abdominal wall which is supplied by those spinal nerves which also convey the visceral afferent fibers supplying the appendix.

True cardiac pain is a relatively rare symptom of cardiac disease. It is less common in valvular disease and obvious hypertrophy or dilatation of the heart than in purely functional derangements. It is localized in the submammary area and is sometimes accompanied

by cutaneous hyperalgesia in the precordial region. The deep pain of angina pectoris is commonly localized in the sternal region. This pain probably has its origin in the aorta or coronary arteries. The referred pain of angina pectoris may be localized in the left breast, along the inner side of the left arm to the elbow or wrist or even to the fingers, and more rarely in the right arm, neck, and jaw. The segments particularly involved are supplied by the lower cervical and upper two or three thoracic nerves. The afferent fibers supplied to the first part of the aorta and coronary arteries through the sympathetic are also components of the upper thoracic nerves.

Careful analysis of the manifestations of pathological lesions in still other visceral organs would reveal visceral pain in some cases unaccompanied by referred somatic hyperalgesia or pain, and in others accompanied by these phenomena, together with muscular guarding or rigidity. The absence or presence of somatic manifestations probably depends mainly on the nature of the visceral lesion, and is not necessarily an indication of the severity of the disease.

The Mechanism of Referred Pain.—Afferent Conduction of Visceral Impulses.—The impulses which give rise to visceral sensations are mediated through the general visceral afferent components of the spinal nerves. Visceral impulses conveyed through afferent components of the vagi probably do not reach the threshold of consciousness. Like the somatic afferent fibers which mediate painful impulses from the periphery, the visceral afferent fibers enter the spinal cord mainly through the lateral division of the posterior spinal nerve roots. Their functional connections in the spinal cord are not fully known. Regarding the afferent conduction pathways involved in vasomotor reactions in the cat, Ranson and Billingsley (1916) found that afferent pressor impulses are conveyed upward in the spinal cord in the apex of the dorsal horn on both sides, but somewhat better homolaterally. Most of these impulses ascend to the vasoconstrictor center in the brain. The depressor impulses are conveyed upward in the ventral part of the lateral funiculus on both sides, but somewhat better contralaterally. This tract, according to Ranson and Billingsley, is located in the same position as the spino-thalamic tract, but the fibers composing it do not ascend beyond the rhombencephalon. They also found that, "in the cat, pain conduction in the spinal cord is bilateral and effected through a series of short relays."

In Spiegel's (1923) experiments on the cat, the afferent conduction of painful impulses produced by injecting barium chloride into the femoral arteries was not affected by transection of the dorsal funiculus of the spinal cord, but the pain reactions elicited by the injection of barium chloride into either femoral artery were diminished following unilateral section of the ventral part of the lateral

funiculus in the lower thoracic segments. Pain reactions were still elicited by the injection of barium chloride into either femoral artery following left hemisection of the spinal cord in the thoracic, and right hemisection in the cervical region. The results of these experiments seem to warrant the conclusion that the conduction of afferent impulses from the peripheral vessels in the cat, particularly those which result in painful sensations, is mediated by crossed conduction pathways which are composed of a series of short relays and lie mainly in the ventral part of the lateral funiculi.

The demonstration of crossed conduction pathways in the spinal cord for afferent impulses arising in the gastro-intestinal canal is more difficult by reason of the fact that the visceral afferent fibers through which these impulses reach the spinal cord enter as high as the fifth (possibly the fourth) thoracic segment. Yet, the experimental results obtained by Spiegel and Bernis (1925) strongly suggest that, in the cat, afferent impulses arising in the gastro-intestinal canal which result in painful sensations are conveyed upward in the spinal cord through the same conduction system which also conveys painful impulses from the peripheral blood vessels.

Certain investigators have assumed that, in man, visceral impulses which result in pain are conducted upward in the spinal cord, at least in part, through the same conduction system which mediates painful impulses from the skin, *viz.*: the lateral spino-thalamic tracts. The evidence on which this assumption is based, however, is not convincing. Inasmuch as afferent visceral impulses, with certain exceptions, do not, under normal physiological conditions, reach the threshold of consciousness, it may be assumed that visceral pain involves hyperexcitation of the neurons in the spinal cord which convey the impulses to the thalamus. Such hyperexcitation may also affect neighboring spinal centers and thus increase the general irritability of the spinal cord, particularly in the segments in which the visceral afferent fibers in question terminate.

Mackenzie's Theory Regarding the Mechanism of Referred Pain.—Mackenzie (1910), like Lange (1871-1876), Head (1889), and Faber (1890) regarded the sensory manifestations of visceral disease, which are referred to the somatic segments corresponding to the segments of the spinal cord with which the afferent fibers supplying the viscus in question are connected, as reflex phenomena. He designated them "viscero-sensory reflexes" and explained them mainly on the basis of the hyperirritability of the spinal cord resulting from exaggerated visceral stimulation.

When a sensory nerve is stimulated in any part of its course, impulses are conveyed to the brain which are similar in kind to those induced by stimulation of the end organ in which the sensory nerve terminates. For example, stimulation of any part of the optic or auditory nerve results in the sensation of light or sound.

In like manner, stimulation of afferent neurons in the spinal cord which are functionally connected with peripheral somatic sensory fibers results in sensations which are referred to the peripheral distribution of the somatic sensory fibers in question.

Under normal physiological conditions, a constant stream of impulses is conveyed by the visceral afferent nerves from the visceral organs to the spinal cord. These impulses are continually playing on the efferent nerves supplying muscle, blood vessels, glands, etc. These processes do not, under ordinary conditions, give rise to sensations. If, however, by reason of a visceral lesion, excessive visceral stimuli reach a certain portion of the spinal cord, this increased stimulation affects neighboring centers. Mackenzie assumed that if neurons in the spinal cord which normally convey cutaneous impulses to the brain are affected in this manner, sensations arise which are referred by the brain, not to the diseased viscus, but to the cutaneous area connected, through its afferent innervation, with the centers in question in the spinal cord. He further assumed that when a portion of the spinal cord is excessively stimulated by reason of visceral disease, it may remain hyperirritable for some time, so that the threshold of stimulation for all the nerves arising from this portion of the spinal cord is lowered. He regarded somatic hyperalgesia and muscular rigidity associated with visceral disease as expressions of such hyperirritability of the spinal cord, the muscular rigidity being due to exaggerated visceromotor reflexes.

Szemzo (1927) advocated the theory of Mackenzie in a slightly modified form. He assumed that the visceral afferent fibers terminate, at least in part, in the posterior cell column in the spinal cord in relation to neurons which are related to the spino-thalamic system, and that it is mainly the hyperirritability of these cells, by reason of excessive visceral stimulation, which explains the phenomenon of somatic hyperalgesia in visceral disease. As long as the threshold of stimulation of these cells for peripheral impulses remains sufficiently low, the slightest stimulation of the peripheral pain-conducting fibers in the somatic segments in question may elicit painful sensations whose intensity is disproportionate to the intensity of the peripheral stimulus. Under certain conditions, pain may be felt in the corresponding somatic segments even in the absence of appreciable somatic stimulation. On this basis, somatic hyperalgesia associated with visceral disease, in the absence of visceral pain, must be regarded as due to hyperexcitation of the spinal cord cells in question through a flow of visceral impulses whose intensity is below the threshold for visceral pain (Goldscheider, 1923). The lingering somatic hyperalgesia, which not infrequently remains after the visceral pain has subsided, in cases of visceral disease, could be explained on the same basis.

The Rôle of Viscero-cutaneous and Viscero-motor Reflexes in Referred Pain.—The above theory affords a plausible explanation of the mechanism of referred pain, but it does not adequately take into consideration the viscerocutaneous and visceromotor reflex phenomena which are perhaps invariably associated with somatic hyperalgesia and probably constitute an important factor in its causation, viz.: vasoconstriction and muscular guarding or rigidity. In certain cases, the hyperalgesic area also exhibits contraction of the erector pili muscles (*cutis anserina*)¹ and secretory activity of the sweat glands.

Wernoe's (1920-1925) clinical and experimental studies have contributed much to our knowledge of the rôle of reflex viscerocutaneous and visceromotor reactions to visceral stimulation in the causation of the sensory phenomena involved in referred somatic hyperalgesia. He observed clinically that cutaneous hyperalgesia is commonly accompanied by cutaneous ischemia, due to peripheral vasoconstriction, and that the area of cutaneous ischemia, in general, coincides exactly with the area of cutaneous hyperalgesia. In certain cases, he also observed localized *cutis anserina* in the hyperalgesic area. In his experience, cutaneous ischemia was so constantly present in areas of hyperalgesia associated with visceral disease that he was able to use it as a diagnostic character, being able, in many cases, to recognize the hyperalgesic area by reason of the cutaneous ischemia when it would have been difficult or impossible to demonstrate hypersensitivity by the more usual methods.

In general, Wernoe's findings regarding the zones of distribution of somatic hyperalgesia in visceral disease corroborate those of Head, Faber, and Mackenzie. He also pointed out that, although somatic hyperalgesia associated with intestinal disease may occur either unilaterally or bilaterally, the zones of cutaneous ischemia are always bilateral if the lesion is located in an unpaired organ and unilateral if the lesion is located in a paired organ.

That cutaneous and other somatic reactions in response to visceral stimulation are reactions of a primitive type is indicated by the facility with which they are elicited in the lower vertebrates. In experiments carried out on fishes, Wernoe (1925) was able to demonstrate peripheral vasoconstriction and pigment reactions in response to localized visceral stimulation. These reactions were not strictly segmental, but usually involved several cutaneous seg-

¹ Ruhmann (1927) cited the case of a patient with duodenal ulcer who, though examined in a warm room, exhibited a zone in the lower abdominal region corresponding to the area of distribution of the eleventh thoracic nerve, in which the skin was cold, pale blue in color, and showed well-developed *cutis anserina*. This phenomenon suggests strong stimulation of the sympathetic fibers supplying the cutaneous blood vessels and erector pili muscles in the area in question. It may be assumed that the afferent impulses involved arose at the site of the duodenal lesion. Similar cases were also reported by Spiegel (1927).

ments, even though the stimulus was applied at a single point. The cutaneous reactions in response to stimulation of an unpaired organ were always bilateral while those in response to stimulation of a paired organ were always unilateral. Since these viscerocutaneous reflexes could be elicited following destruction of the spinal cord in the corresponding segments, Wernoe interpreted them as axon reflexes mediated through a single sympathetic neuron which sends processes both to a visceral organ and the skin. The visceromotor reactions (muscular contraction) which commonly accompany the viscerocutaneous reactions could be elicited only while the spinal cord was intact. These reactions involve reflexes which are carried out through the spinal cord.

Cutaneous stimulation in these animals also elicited vasomotor reactions in the viscera, producing visceral hyperemia in some instances, and visceral ischemia in others. Vasodilator visceral reflexes were obtained only in the intact animal. Obviously, they are carried out through the spinal cord. Vasoconstrictor visceral reflexes were also obtained following destruction of the spinal cord; consequently, Wernoe also interpreted these reactions as axon reflexes.

On the basis of the experimental results cited above, and the results of his earlier clinical studies, Wernoe concluded that cutaneous hyperalgesia probably does not depend on the effect of visceral stimulation of neurons in the spinal cord, but has its origin in changes brought about in the skin through viscerocutaneous reflexes. In support of this conclusion from the clinical side, he pointed out that under certain conditions sympathetic stimulation alone gives rise to pain. For example, if the fingers are subjected to cold they gradually become ischemic and painful until, with complete anemia, the anesthetic stage is reached. If the hand is then warmed, the fingers again become painful until circulation is restored to normal. As the fingers are subjected to cold, vasoconstriction is brought about through reflex stimulation of the vasomotor fibers. The consequent pain is the result of the stimulating effect of the ischemic conditions of the surrounding tissues and the hypertonic state of the smooth muscle in the vessel walls on the sensory end organs. In like manner he assumed that the cutaneous pain receptors may be stimulated by the ischemia brought about in the skin through viscerocutaneous reflexes.

That vasoconstriction, either by reason of hypertension or spastic contraction of the smooth muscle in the vessel walls or the consequent ischemia of the adjacent tissue, is a major factor in the production of pain referable to the blood vessels is well known. Peripheral vasoconstriction elicited reflexly through the sympathetic innervation of the blood vessels in the somatic area involved, by impulses arising in a diseased viscus, may, therefore, be regarded

as a contributing factor in the production of hyperalgesia in the same area. Likewise, reflex contractions of the erector pili muscles elicited in the same manner may well be regarded as a contributing factor in the hypersensitivity of the area involved, especially to light touch and even air currents playing on the skin.

Spastic contraction or hypertension of skeletal muscles may give rise to pain by reason of its stimulating effect on the sensory receptors in the muscle tissue. The reflex muscular guarding or rigidity which accompanies somatic hyperalgesia in many cases of visceral disease, *e. g.*, acute appendicitis and gastric ulcer, may, therefore, in all cases in which it is well developed, be regarded as a contributing factor in the production of the associated hyperalgesia and the muscular tenderness and pain. Since painful stimuli are the most provocative causes of reflexes, acutely tender muscles tend to remain permanently contracted. This tendency probably is an important factor in the maintenance of muscular rigidity, in many cases, after the exaggerated visceral stimulation has subsided. As long as the muscle remains sufficiently spastic it also remains hypersensitive.

The Reflex Mechanism Involved.—The reflex arcs through which the peripheral vasomotor and pilomotor reactions are mediated comprise a general visceral afferent neuron, through which afferent impulses are conveyed from the site of the visceral lesion to the spinal cord, a visceral efferent neuron, located in the intermediolateral cell column, and a sympathetic neuron, located in the corresponding ganglion of the sympathetic trunk, through which efferent impulses are conveyed to the smooth muscle in question. In so far as cutaneous impulses are a factor in the production of referred pain, they are conveyed by the pain-conducting fibers distributed to the skin and cutaneous blood vessels.

Doubtless, the reflexes involved in muscular guarding and rigidity are mediated in part through reflex arcs composed of a general visceral afferent neuron, through which afferent impulses are conveyed from the site of the visceral lesion to the spinal cord, an intercalated neuron in the gray matter, and a somatic efferent neuron located in the same segment of the spinal cord, through which efferent impulses are conveyed to the muscle. Inasmuch as skeletal muscles also receive sympathetic fibers (see Chapter XV), it seems not improbable that reflex arcs whose efferent limbs consist, not of a somatic efferent neuron, but of a visceral efferent and a sympathetic neuron, may also play a rôle in the phenomenon of muscular rigidity associated with visceral disease. The chief objection to this view consists in the fact that repeated attempts to elicit either tonic or motor reactions in skeletal muscles by artificial stimulation of sympathetic fibers alone have yielded only negative results. Nevertheless, experimental evidence in support of the theory that the sympathetic innervation of skeletal muscles is a

factor in the production and maintenance of muscle tonus is not wanting (see Chapter XV). Consequently, it seems highly probable that viscerosympathetic reflexes may be a factor, particularly is sustained hypertonus, such as is exhibited in muscular guarding or rigidity in cases of visceral disease. In so far as impulses arising in the muscles play a part in the production of referred pain and the maintenance of muscular rigidity, they are conveyed by the sensory fibers which terminate in the muscles. The reflex arcs through which the influence of these impulses in maintaining muscular rigidity is exerted are simple spinal reflex arcs.

That all the nervous reactions involved in the referred somatic manifestations of visceral disease are facilitated by the hyperirritability of the centers in question in the spinal cord produced by the exaggerated visceral stimulation seems highly probable. Furthermore, the degree of hyperirritability produced in the spinal cord may be a determining factor in the intensity of both the direct visceral pain and the referred pain.

CHAPTER XVIII.

VAGOTONIA AND SYMPATHETICOTONIA.

GENESIS OF THE CONCEPTION, AND DEFINITION.

SINCE the visceral organs are innervated through both the sympathetic and parasympathetic divisions of the autonomic nervous system, which are mutually antagonistic in function, any disturbance of the functional balance of the sympathetic and parasympathetic nerves must result in disturbances of visceral functions. This was early recognized by von Noorden (1892), who called attention to various clinical conditions associated with increased vagus irritability and designated them *vagus neuroses*. The clinical conception of vagotonia and sympatheticotonia was first formulated by Eppinger and Hess in 1909 and further elaborated by them in a series of later papers. They observed that adrenalin exerts a stimulating effect on the sympathetic nerves similar to the effect of pilocarpin on the parasympathetic nerves. They found, in many instances, that if adrenalin produced strong sympathetic stimulation, pilocarpin did not stimulate nor did atropin paralyze the parasympathetic nerves. Likewise, if pilocarpin or atropin produced a strong parasympathetic reaction, the injection of adrenalin was without effect on the sympathetic nerves. On the basis of extensive observations on the effects of these drugs in man, they concluded that all persons who react strongly to pilocarpin and atropin are relatively insensitive to adrenalin, and all persons who react strongly to adrenalin are relatively insensitive to atropin and pilocarpin. On the basis of this conclusion, they assumed that clinical cases exhibiting a functional imbalance between the sympathetic and parasympathetic nerves could be classified as vagotonic or sympatheticotonic, depending on the relative reactivity of the parasympathetic and sympathetic nerves. They also recognized more or less definite symptom complexes which are usually associated with exaggerated reactivity of the parasympathetic and sympathetic nerves respectively. They conceived of absolute vagotonia as consisting in actual hyperreactivity or exaggerated tonus of the parasympathetic, and absolute sympatheticotonia as consisting in hyperreactivity or exaggerated tonus of the sympathetic division of the autonomic nervous system. According to their conception, relative vagotonia may exist in the absence of exaggerated parasympathetic tonus if the reactivity of the sympathetic nerves is subnormal or

there is a deficiency in the chromaffin system. Likewise, relative sympathicotonia may exist in the absence of exaggerated sympathetic tonus if the reactivity of the parasympathetic nerves is subnormal. In either case, vagotonia and sympathicotonia involve an increase in functional activity in the respective division of the autonomic nervous system, which may affect the entire system or only a portion of it. Eppinger and Hess stated specifically that autonomic imbalance need not involve the entire autonomic system, and admitted the occurrence of localized vagotonia, but they repeatedly expressed the opinion that exaggerated tonus in one division of the autonomic nervous system precludes heightened reactivity in the other division.

According to the original conception of Eppinger and Hess, the entire sympathetic and parasympathetic systems are tonically stimulated and sustain a physiological balance which may be shifted in favor of one or the other system by abnormal functional conditions. Exaggerated tonus of either system does not necessarily imply hyperirritability of the nerve centers involved, but may be brought about by a superabundance of stimulating substances in the blood. In general, they regarded vagotonia as characterized by hyperreactivity to parasympathetic stimulation and sympathicotonia as characterized by hyperreactivity to sympathetic stimulation of all the organs innervated through the autonomic nervous system, although, as stated above, they recognized the possibility of localized vagotonia.

CRITIQUE OF THE CONCEPTION.

On the basis of an extensive study of the effects of adrenalin, pilocarpin and atropin in clinical conditions, Petren and Thorling (1911) pointed out that, in certain diseases in which exaggerated parasympathetic tonus is usually apparent, *e. g.*, gastric and duodenal ulcer, bronchial asthma, etc., a small percentage of the patients, as judged by their reactions to these drugs, exhibits exaggerated sympathetic tonus, and a somewhat larger percentage reacts strongly to adrenalin and also to pilocarpin and atropin, thus proving that the same individual may exhibit heightened reactivity of both divisions of the autonomic nervous system. Whereas Eppinger and Hess assumed that heightened reactivity to atropin or pilocarpin must be due either to diminished sympathetic or exaggerated parasympathetic tonus, Petren and Thorling pointed out that the observed reactions to parasympatheticomimetic and sympatheticomimetic drugs can be explained more satisfactorily, in certain cases, on the assumption of heightened irritability of both the parasympathetic and sympathetic nerves. The latter authors

agreed with Eppinger and Hess, however, regarding the existence of vagotonia and sympatheticotonia as recognizable functional states which represent deviations from the normal functional balance of the autonomic nervous system.

Not a few more recent investigators, on the basis of both experimental and clinical findings, have supported the general theory of vagotonia and sympatheticotonia, either as advanced by Eppinger and Hess or in a somewhat modified form; others have rejected it *in toto*, mainly by reason of the lack of a clear-cut differentiation between the symptoms associated with vagotonia and those associated with sympatheticotonia, and the amphitropic action of certain drugs and certain of the natural hormones.

The findings of Petren and Thorling cited above, according to which certain individuals who, by reason of a more or less definite symptom-complex, seem to exhibit vagotonia also react strongly to sympathetic stimulation, and others who, by reason of an equally definite symptom-complex, seem to exhibit sympatheticotonia also react strongly to parasympathetic stimulation have been confirmed by not a few later investigators. Furthermore, it has also been amply demonstrated that the symptom-complexes commonly associated with certain diseases which, according to the theory of Eppinger and Hess, are related to vagotonia, also include symptoms which suggest exaggerated reactivity of the sympathetic nerves. Likewise, symptom-complexes associated with diseases which, according to this theory, are related to sympatheticotonia also include symptoms which suggest hyperreactivity of the parasympathetic nerves. For example, the dominant symptoms of pulmonary tuberculosis, particularly during the second and third stages of the disease, usually indicate vagotonia; yet, the gastro-intestinal symptoms sometimes suggest exaggerated sympathetic tonus. Likewise, the dominant symptoms of hyperthyroidism, viz.: tachycardia, increased metabolism, fever, etc., suggest sympatheticotonia; yet, gastro-intestinal hypermotility, so common in this disease, involves exaggerated parasympathetic reactivity. Unusually strong reactions to either parasympatheticomimetic or sympatheticomimetic drugs or both have also been reported repeatedly in certain individuals apparently in good health who exhibited no objective evidence of a functional autonomic imbalance.

The symptom-complex commonly associated with hyperthyroidism has frequently been cited as incompatible with the theory of vagotonia and sympatheticotonia. According to Eppinger and Hess, patients with exophthalmic goiter may be classified as vagotonic or sympatheticotonic on the basis of gastro-intestinal hypermotility and tachycardia respectively. Now it is well known that many cases of exophthalmic goiter exhibit both gastro-intestinal hypermotility and tachycardia at the same time; consequently, it

cannot be assumed, on basis of these symptoms, that either vagotonia or sympathicotonia exists in these cases; yet, it cannot be denied that, in many cases of this disease, the dominant symptom-complex, including persistent diarrhea, gastric hyperacidity, vomiting, vasodilatation, and circumscribed edema, strongly suggest parasympathetic hyperirritability. Absolute vagotonia or sympathicotonia, in the sense of Eppinger and Hess, probably is never observed in cases of exophthalmic goiter.

Eppinger and Hess also regarded eosinophilia as a sign of vagotonia. Among the various conditions with which eosinophilia is associated may be mentioned bronchial asthma, skin diseases, intestinal parasitism, etc. Certain of the conditions of bronchial asthma, viz.: spasm of the bronchial musculature and vasodilatation of the bronchial mucosa, can readily be explained on the basis of vagotonia. These conditions can also be relieved by the administration of atropin which diminishes parasympathetic tonus or adrenalin which increases sympathetic tonus. Dermography of the dilator type and urticaria are not uncommonly associated with a liability to eosinophilic skin eruptions. They have also been regarded as signs of vagotonia. The evidence in support of this view, however, can hardly be regarded as conclusive (Langdon Brown, 1923).

It has been assumed by some that intestinal parasites bring about eosinophilia by exciting the parasympathetic nerves. That the parasympathetic innervation of the gastro-intestinal canal is overstimulated in the presence of intestinal parasites is indicated by increased peristalsis and spastic intestinal contractions which sometimes result in spastic constipation. Eosinophilia also occurs in conditions of known toxic origin. It seems not improbable, therefore, that the toxic effect of the intestinal parasites might result in both parasympathetic stimulation and eosinophilia. Although it must be admitted that it is not infrequently associated with other evidences of parasympathetic hyperreactivity, there is no conclusive evidence that eosinophilia occurs only in association with vagotonia. Yet, it has been claimed that eosinophilia is never associated with sympathicotonia.

One of the most striking symptom complexes indicative of general vagotonia is that associated with spastic constipation which has been regarded by most investigators in this field as a purely vagotonic disease (Müller, 1924; Bennhold and Hauptstein, 1928). Even Ganter (1925), who opposed the theory of vagotonia and sympathicotonia, admitted that spastic constipation, particularly the hyperkinetic form, is usually associated with a condition of hyperirritability throughout at least the greater part of the parasympathetic system. In a recent study of frank cases of spastic constipation, Bennhold and Hauptstein (1928), using the pupillary

reaction as an index, observed the expected parasympathetic response to pilocarpin and atropin in every case.

In elaborating their theory of vagotonia and sympatheticotonia, Eppinger and Hess gave little attention to the vasomotor reactions to changes in the functional autonomic balance. Yet, the functional condition of the cardiovascular system must be regarded as one of the best criteria of the functional condition of the autonomic nervous system. Ganter (1925) expressed the opinion that the existence of vagotonia or sympatheticotonia could, in certain clinical conditions, be determined only on the basis of vasomotor reactions. According to his conception, vagotonia cannot exist coincident with increased tonus of the musculature of the blood vessels, even though all other symptoms suggest exaggerated parasympathetic reactivity, since vasoconstriction involves sympathetic stimulation. He also pointed out that the pulse-rate, which is not infrequently regarded as an index of the sympathetic-parasympathetic balance, is affected reflexly by a wide variety of conditions. For example, increased blood pressure commonly results in retardation and decreased blood pressure in acceleration of the cardiac rhythm. Yet, the cardiac accelerator fibers, like the vasomotor fibers are sympathetic. The vasomotor reactions during infectious fevers are also significant. Blood pressure is usually reduced under these conditions. Although it does not always parallel the tonic state of the vascular musculature, it is evident in most cases that when the blood pressure is low during infectious fevers the vascular musculature is in a state of low tonus. According to the theory of Eppinger and Hess, this diminution of the tonus of the vascular musculature would have to be regarded as evidence of exaggerated parasympathetic tonus. On the other hand, the increase in heart rate which usually occurs during fever would have to be regarded as evidence of exaggerated sympathetic tonus. In view of the common occurrence of diminished blood pressure coincident with a rise in the heart-rate, Ganter maintained that it would be futile to speak of either vagotonia or sympatheticotonia in such cases. This, however, does not invalidate the theory of vagotonia and sympatheticotonia. The increased heart-rate associated with low blood pressure is determined, at least in part, by reflex stimulation. There are also notable exceptions to the general rule that the increase in the heart-rate during fever parallels the rise in temperature. For example, in tuberculosis, the increase in the heart-rate during fever is usually less marked than in other infectious diseases during periods of the same degree of temperature. This is in full accord with the other evidences of vagotonia apparent in tuberculous patients. Furthermore, as was pointed out by Pottinger (1917), vagotonia is not a constant condition in tuberculosis. According to his findings in patients with pulmonary tuberculosis, sympathetic

tonus is increased during toxemia by reason of central stimulation and the reflex effect of the inflammation in the lung; consequently, sympathetic tonus may predominate during toxemia. After the toxemia subsides, a condition relative to vagotonia again obtains in most cases. It is also well known, particularly with regard to the vascular system, that the same functional balance between the sympathetic and parasympathetic nerves does not obtain throughout the entire autonomic nervous system. In a series of studies bearing on the interactions between the peripheral and splanchnic components of the autonomic nervous system in relation to the peripheral and splanchnic blood vessels, Müller (1926) has shown that, in general, the same stimulus which brings about a change in the functional autonomic balance at the periphery induces a corresponding change in the opposite direction in the splanchnic area, and *vice versa*. The simultaneous occurrence of certain symptoms referable to exaggerated parasympathetic tonus in the peripheral area, or *vice versa*, in certain diseases, may probably be explained on the same basis.

The inherent functional character of the sympathetic and parasympathetic divisions of the autonomic nervous system respectively has its basis in phylogenetic and anatomical differences and the functional requirements of the organs and tissues innervated. The conception of the antagonistic action of the sympathetic and parasympathetic nerves supplying any visceral organ rests on a firm experimental basis. In general, the effect of stimulation of one division of the autonomic system is the equivalent of the effect of inhibition of the other. Yet, the factors in the activation of either the sympathetic or parasympathetic nerves, under normal or pathological conditions, are not fully known. That hormones produced by certain of the endocrin glands, *e. g.*, the adrenals and thyroid, stimulate the sympathetic nerves is well known. Probably hormones also play a rôle in the activation of the parasympathetic nerves. Theoretically, it seems not improbable that overactivity of one or the other of the endocrin glands might also result in exaggerated tonus of one or the other division of the autonomic system. The stimulating effect of a given hormone is, however, not strictly limited to one division of the autonomic system in all cases. For example, adrenalin, which, in appropriate dosage, is a most powerful sympathetic stimulant, bringing about a sharp rise in blood pressure, in minimal doses, brings about a fall in blood pressure (Hoskins and McClure, 1912). Neither are drugs which are commonly regarded as specific either for the sympathetic or parasympathetic nerves in all cases limited in their action to one effect. For example, atropin in small doses stimulates, but in large doses paralyzes the parasympathetic nerves; yet, for all practical purposes the paralyzing effect of atropin on the parasympathetic

nerves is decisive. Likewise, the hormones, regardless of their amphitropism, in the concentration in which they are normally present in the body, exert mainly a single effect, *i. e.*, their stimulating effect on one or the other divisions of the autonomic system is predominant. Unfortunately, there is no hormone available which is known to be essentially a parasympathetic stimulant. Consequently, studies of the effect of hormones in producing sympathetic-parasympathetic imbalance must be one-sided. Nevertheless, studies involving the effect of adrenalin alone have yielded valuable data. On the other hand, many of the data obtained in such studies are not unequivocal.

In order to obtain trustworthy results in studies involving the reactivity of the sympathetic nervous system to adrenalin, it is necessary to guard against certain possible sources of error. In the first place, it is important that the same reaction to adrenalin be observed in every case, since the various reactions to adrenalin may, under certain conditions, be dissociated. For example, adrenalin glycosuria may be present in certain cases in the absence of tachycardia. Likewise, the administration of adrenalin results in increased heart action in certain individuals without a corresponding rise in blood pressure. Still other individuals exhibit a marked rise in blood pressure, in response to adrenalin, without a corresponding increase in cardiac rhythm and without glycosuria (Balint, 1927). Because of the inconstancy of certain adrenalin reactions, it is also important to select those reactions which are most constant. Failure to observe this precaution has given rise to not a little confusion regarding the value of adrenalin reactions as an index of sympathetic reactivity. Hyperglycemia, glycosuria, and tachycardia are reactions which depend not only on the stimulating effect of adrenalin on the sympathetic nerves, but also on the condition of the kidneys, liver, heart, and cerebrospinal nervous system. Neither is sympathetic stimulation the only factor involved in increased blood pressure. The blood vessels always contract, however, in response to adrenalin by reason of its stimulating action on the sympathetic fiber terminations in the vessel musculature, and such vasoconstriction commonly results in a rise in blood pressure. Increased blood pressure is, therefore, one of the most constant reactions to sympathetic stimulation by means of adrenalin, and constitutes one of the most certain criteria of sympathetic reactivity.

The choice of a method for the administration of adrenalin is also a matter of great importance. A given dose of adrenalin injected subcutaneously or intramuscularly does not produce the same effect as if injected intravenously. The reaction in the former case depends not only on the reactivity of the sympathetic nerves but also on the rate of absorption of the hormone. Inasmuch as both

these factors are unknown, the resultant rise in blood pressure cannot be regarded as a true index of the functional state of the sympathetic nervous system. Doubtless, herein lies one of the chief causes of the diverse results obtained in attempts, by the use of adrenalin, to determine the functional condition of the sympathetic nervous system in any given disease. In order to obtain comparable results, the adrenalin must be administered in the same way in every case, preferably by intravenous injection (Csepai, 1927; Balnit, 1927). When administered in this manner, it usually results in greater sympathetic excitation in sympathetotonic and less in vagotonic than in normal individuals.

Although the results of the majority of the more recent studies bearing on the general problem of the functional balance of the autonomic nervous system do not indicate the occurrence of pure vagotonia and sympathetotonia, except possibly in rare instances, the conception of vagotonia and sympathetotonia remains a useful conception and affords an intelligent explanation of not a few phenomena involved in functional visceral disorders and organic diseases. The findings of Eppinger and Hess have not been fully corroborated, and it must be conceded, in view of all the data available at present, that vagotonia and sympathetotonia are less clearly differentiated, in the majority of cases, than was assumed by these authors. Furthermore, some of the conditions which they regarded as the results of sympathetic-parasympathetic imbalance probably can be explained more satisfactorily on some other basis. Nevertheless, the existence of vagotonia and sympathetotonia cannot be denied. With the accumulation of further experimental and clinical data, these conceptions are also becoming more clearly delimited.

NATURE AND CAUSES OF SYMPATHETIC-PARASYMPATHETIC IMBALANCE.

In the light of our present knowledge regarding vagotonia and sympathetotonia, it is not without interest to recall that von-Noorden (1892) regarded sympathetic-parasympathetic imbalance as a visceral neurosis associated with neuroses of other types. That it is not infrequently associated with constitutional deficiencies is well known. Nervous and mental diseases are frequently accompanied by far-reaching disturbances of visceral functions in which sympathetic-parasympathetic imbalance plays an important rôle. Temporary psychic and emotional disturbances of a purely functional character are, in many instances, also accompanied by parasympathetic hyperirritability; less frequently by sympathetic hyperirritability.

The data available at present do not warrant the conclusion that

the autonomic centers in the brain stem are directly connected functionally with the cortex. The highest known central autonomic centers are located in the hypothalamic portion of the diencephalon (Chapter III). That these and lower autonomic centers are influenced by cortical and subcortical central nervous processes cannot be denied. Yet, to what extent sympathetic-parasympathetic imbalance is due to cerebral influences and to what extent it is brought about reflexly or as the result of pathological changes in the autonomic nervous system cannot be stated at present. The data bearing on the relation of sympathetic-parasympathetic imbalance to nervous and mental disorders strongly suggest, however, that in those cases in which there is a constitutional central nervous deficiency, this deficiency is an important factor in the genesis of the autonomic imbalance.

Vagotonia is commonly associated with hyperacidity. The results of recent studies bearing on the relationship of changes in the acid-base equilibrium to disturbances in the functional equilibrium of the autonomic nervous system have contributed largely to a better understanding of the rôle of sympathetic-parasympathetic imbalance in disease. Kraus and Zondek (1922, 1924) forcibly called attention to the influence of electrolytes on the autonomic nervous system and emphasized the importance of the acid-base balance in all diseases in which the autonomic system is directly involved.

The results of recent clinical studies by Hollo and Weiss (1925) have shown that calcium chloride administered intravenously in therapeutic doses reduces the bicarbonate content of the blood plasma, but increases the hydrogen-ion concentration of the blood and the alveolar carbon dioxide tension. Calcium chloride and calcium lactate administered by mouth also reduce the bicarbonate content of the blood plasma. These results are in full agreement with those of Fürst (1925) and others obtained in animal experiments, and show clearly that the acid-base balance can be changed in the direction of acidity by the administration of calcium. Likewise, an increase in the potassium-ion concentration results in a change in the acid-base balance in the direction of alkalinity.

That changes in the acid-base balance result in changes in the functional balance between the sympathetic and parasympathetic systems has been amply demonstrated. The results of experiments involving the stimulating effect of adrenalin on the sympathetic nerves proves conclusively that the effect of adrenalin is influenced by the chemical reaction of the fluids circulating through the organs in question. In the experiments of Snyder and Andrews (1919), Snyder and Campbell (1920), and Snyder and Martin (1922), adrenalin perfused through the portal system in turtles resulted in dilatation of the blood vessels when the hydrogen-ion concentration of the perfusion fluid was low. Certain experimental data cited

by Balint also indicate a greater rise in blood pressure in response to a given dose of adrenalin when the reaction of the blood is alkaline than when the acid-base balance is shifted toward the acid side. In some instances, when the reaction of the blood tended toward the acid side, the administration of adrenalin elicited no rise in blood pressure. In perfusion experiments on the frog's heart, Atzler and Müller observed inhibition, *i. e.*, a parasympathetic reaction, when the perfusion fluid was acid, and acceleration, *i. e.*, a sympathetic reaction, when the perfusion fluid was alkaline.

In a recent clinical study, Weiss and Benkovics (1925) found that the effect of adrenalin on blood pressure was reduced following the administration of calcium chloride which, as stated above, shifts the acid-base balance of the blood toward the acid side. This result is in full accord with actual clinical findings. Patients with hyperthyroidism commonly exhibit a shifting of the acid-base balance toward the alkaline side. They also exhibit increased sympathetic reactivity to adrenalin. In general, the degree of change toward the acid side corresponds to the degree of improvement. The decrease in the reactivity of the sympathetic nerves to adrenalin also corresponds to the reduction in the alkalinity of the blood (Csepai, Hollo, and Weiss, 1925). Likewise, patients suffering with diseases which are commonly associated with hyperacidity, *e. g.*, bronchial asthma, diabetes insipidus, etc., rarely, if ever, exhibit increased sympathetic reactivity to adrenalin. In many cases, the reactivity of the sympathetic nerves to adrenalin is actually subnormal (Balint, 1927). Patients with diabetes mellitus exhibit a wide range of variation in the reactivity of the sympathetic system to adrenalin. In a study involving comparison of sympathetic reactivity and the acid-base reaction of the blood in diabetic patients, Csepai, Hollo, and Weiss (1925) found that sympathetic reactivity to adrenalin was subnormal in those exhibiting hyperacidity, but increased in those who had been subjected to massive sodium bicarbonate treatment. In certain cases in which they found subnormal sympathetic reactivity before treatment, adrenalin elicited a normal or exaggerated response after alkaline therapy. These results are in full accord with the results of animal experimentation cited above and strongly support the theory that sympathetic tonus is increased by a change in the acid-base balance in the blood toward the alkaline side and parasympathetic tonus is increased by a change in the acid-base balance toward the acid side.

If such is the case, we should expect to find evidence of hyperacidity in all cases in which vagotonia exists. The data bearing on this point are still meager, but they afford evidence which is strongly suggestive. The results of recent studies have shown that chronic gastric and duodenal ulcer is almost invariably associated with vagotonia and hyperacidity (Fokin, 1925; Lande, 1926;

Simnitzky, 1927; Balint, 1927; and others). In certain cases of cholelithiasis, the dominant symptoms resemble very closely those of gastric ulcer. This is true particularly of the reflex reactions of the stomach, including hypermotility and changes in gastric secretory activity which are manifestations of vagotonia. Although vagotonia is usually demonstrable in cases of cholelithiasis, the hydrogen-ion concentration of the blood falls within the normal range in many cases. In a recent clinical study of 14 patients with cholelithiasis, involving determination of the hydrogen-ion concentration of the blood and the elimination of alkali through the kidneys, Balint (1927) found that, although the hydrogen-ion concentration of the blood did not deviate beyond the normal limits in any of the 13 cases in which it was determined, the urine did not become alkaline or only slightly so following the injection of sodium bicarbonate in 9 cases, showed a neutral reaction in 1, and an alkaline reaction in the other 4. The majority of these cases (9 out of 14) exhibited alkali retention which, according to Balint, is associated with an acid condition of the tissues. It must be admitted, therefore, that the tissues were more acid than normal in these cases, although hyperacidity was not demonstrable in the blood. The results obtained in a limited number of cases of bronchial asthma, in general, corroborate the above findings in cases of cholelithiasis. On the basis of these findings, Balint concluded that some degree of hyperacidity is a common accompaniment of vagotonia, although the hydrogen-ion concentration of the blood may not deviate beyond the normal limits.

The adaptive compensatory reaction between the peripheral and splanchnic blood vessels constitutes another important factor in the causation of changes in the tonic balance between the sympathetic and parasympathetic systems. That peripheral vasoconstriction is commonly accompanied by splanchnic vasodilatation is a fact of common knowledge. As stated above, E. F. Müller (1926) has shown that the stimuli which elicit vasoconstriction at the periphery also elicit vasodilatation in the splanchnic area, and *vice versa*. These changes are accompanied by corresponding changes in the permeability of the blood vessels and the distribution of leukocytes. The area in which sympathetic tonus predominates exhibits leukopenia; that in which parasympathetic tonus predominates exhibits leukocytosis; consequently, leukopenia and leukocytosis parallel compensatory vasoconstriction and vasodilatation and may be regarded as indices of the functional autonomic balance in the respective areas.

In a study involving the effect of changes in the functional autonomic balance, Bueno (1925) obtained certain data which seem to indicate that fluctuations in the differential leukocyte count are also correlated with changes in the tonic balance between the

sympathetic and parasympathetic systems. According to his findings, the polymorphonuclears react first to the vasomotor disturbance. If the disturbance is severe, mononuclear leukocytes also react. In the latter case, the polymorphonuclears and lymphocytes disappear from the peripheral blood and accumulate in the splanchnic area, leaving only the mononuclears at the periphery. The results of these studies are of peculiar interest in view of the original contention of Eppinger and Hess, that eosinophilia is correlated with vagotonia.

On the basis of his experimental and clinical observations, E. F. Müller concluded that the peripheral and splanchnic blood vessels react like parallel end organs to a single stimulus which results in sympathetic stimulation in one area and parasympathetic stimulation in the other. This, however, occurs only when the local normal autonomic balance has been disturbed. The peripheral and splanchnic blood vessels never exhibit the same sympathetic-parasympathetic imbalances, *i. e.*, disturbances in the functional balance between the sympathetic and parasympathetic systems do not affect the peripheral and splanchnic blood vessels in the same manner, but increased sympathetic tonus in the one area is accompanied by decreased sympathetic tonus or increased parasympathetic tonus in the other, and *vice versa*.

The peripheral and splanchnic areas are so intimately connected with each other through this autonomic regulatory mechanism that the slightest change in the autonomic balance at the periphery gives rise to a corresponding change in the opposite direction in the splanchnic area, and *vice versa*, under both physiological and pathological conditions. Disease processes may result either in chronic fixation of an abnormal sympathetic-parasympathetic balance or in increased instability of the autonomic nervous system, either of which conditions might result in inadequate compensatory reactions or overcompensation, giving rise to abnormal conditions of blood pressure (E. F. Müller, 1926).

Sympathetic-parasympathetic Imbalance and Disease.—That the dominant symptoms of many of the common diseases are manifestations of hyperactivity either of the sympathetic or parasympathetic nerves is well known. For example, the dominant symptoms of exophthalmic goiter, *viz.*: tachycardia, exophthalmos, increased metabolism, fever, etc., are manifestations of exaggerated sympathetic stimulation. This, however, does not warrant the conclusion that sympathetic hyperactivity is a factor in the genesis of this disease. Since the thyroid secretion is a sympathetic stimulant, sympathicotonia associated with thyroid hyperactivity may be regarded as a result and not as a cause of the disease. Nevertheless, sympathicotonia must be recognized as an important factor in the dominant symptom-complex.

The dominant symptoms of bronchial asthma, viz.: the respiratory disturbances due to spasm of the bronchial musculature and edema of the bronchial mucosa are manifestations of parasympathetic hyperactivity. In this instance, the relationships are such as to suggest that vagotonia is an important factor in the etiology of the disease.

Not a few recent investigators have also emphasized the rôle of vagotonia in the genesis of gastric and duodenal ulcer. Mucci (1926) advanced certain data which he interpreted as indicating that ulcer formation is a direct result of a loss of balance between the sympathetic and parasympathetic innervation of the digestive tube, which may be of emotional or toxic origin or both, but develops only with a constitutional tendency to gastro-intestinal neuroses. On the basis of extensive clinical and experimental studies, E. F. Müller (1926) advanced the opinion that chronic gastric and duodenal ulcers have their cause in a chronic constitutional disorder which involves predominance of parasympathetic tonus. In such individuals, according to his view, slight irregularities in the general body economy, *e. g.*, dietary indiscretions, psychic disturbances, exposure, etc., which under normal functional conditions of the autonomic nervous system give rise to visceral disturbances which are relatively unimportant and of short duration, may, by reason of the constitutional disorder, result in long-continued excitation of the hyperirritable components of the autonomic innervation of the organ in question. Consequently, strong peripheral stimulation may result in gastro-intestinal hyperexcitation, the duration of which cannot be foretold. In certain individuals, according to Müller, such gastro-intestinal hyperexcitation may actually give rise to gastric or duodenal ulcer.

Lande (1926) was able to demonstrate vagotonia in 75 per cent of gastric and duodenal ulcer patients. Fokin (1925) reported similar findings. Simnitzky (1927) also observed other signs of vagotonia in a high percentage of his patients with gastric and duodenal ulcer and recognized the autonomic functional imbalance as a factor in the etiology of the disease, but emphasized hyperacidity as a causative factor in vagotonia. Balint (1927) also emphasized the constant association of hyperacidity with vagotonia in ulcer patients, and pointed out that the majority of these patients exhibit alkali retention, indicating a hyperacid condition of the tissues. The fact that the sympathetic-parasympathetic balance may be shifted by measures which bring about an increase or a decrease in the hydrogen-ion concentration of the blood also seems to support the theory that hyperacidity is a factor in the genesis of vagotonia. It is not improbable, however, as Balint also suggested, that alkali retention may depend in a large measure on vagotonia. Neither do these observations minimize the importance of an under-

lying constitutional disorder in the etiology of ulcerative gastrointestinal disease.

The occurrence of vagotonia during pregnancy and its possible rôle in the etiology of eclampsia has recently been the subject of extensive investigation and some controversy. Changes in the functional balance between the sympathetic and parasympathetic systems during pregnancy are not uncommon. According to not a few recorded observations, the functional reactions of some of the organs, during this period, suggest vagotonia; those of other organs suggest sympatheticotonia. For example, the effect of adrenalin on the blood-pressure curve indicates exaggerated parasympathetic reactivity, while glycosuria suggests exaggerated sympathetic reactivity.

On the basis of results obtained in a series of studies involving the effect of adrenalin administered subcutaneously in pregnant women on blood pressure, Louros (1923) described "vagotonia of pregnancy." In women who before pregnancy exhibited normal sympathetic-parasympathetic balance, the administration of adrenalin during pregnancy resulted in decreased blood pressure. This effect became more marked as pregnancy advanced. In women who exhibited some degree of sympatheticotonia before pregnancy, the administration of adrenalin during pregnancy resulted in a blood-pressure curve which indicated gradual compensation by increasing parasympathetic tonus. In women who exhibited vagotonia before pregnancy, the administration of adrenalin resulted in a more marked decrease in blood pressure. Louros regularly found vagotonia more marked in eclampsia than during pregnancy. In a more recent study (1926), he emphasized the importance of vagotonia as a factor in the etiology of eclampsia.

Certain other investigators have failed to corroborate these findings. In a recent critique of Louros' work, Schlossmann (1928) rejected the entire conception of a vagotonia of pregnancy as incompatible with his own experimental findings in pregnant animals. He also pointed out that not infrequently the blood pressure actually rises during pregnancy and particularly in eclampsia. According to Louros, this increased blood pressure is the result of an adaptive, reflex compensatory reaction on the part of the peripheral blood vessels. As is well known, vasodilatation in the splanchnic area is always compensated, at least in part, by reflex peripheral vasoconstriction. Such reflex vasoconstriction in the peripheral area, however, does not usually result in full compensation. According to Louros' conception, it must be assumed that reflex peripheral vasoconstriction may actually result in over-compensation in pregnancy and the eclamptic state. The fact that the results of the administration of adrenalin, in his studies, seemed to indicate exaggerated parasympathetic tonus throughout

the entire vasomotor mechanism during pregnancy led him to deny the existence of exaggerated sympathetic tonus even in the peripheral area. In view of the findings of E. F. Müller, referred to above, regarding a regulatory mechanism through which stimuli which result in the dominance of parasympathetic tonus in the splanchnic area bring about the dominance of sympathetic tonus in the peripheral area, and *vice versa*, exaggerated reactivity of the vasoconstrictor nerves in the peripheral area during pregnancy can readily be explained as an adaptive compensatory reaction which results in overcompensation.

Pharmacodynamic Criteria of Sympathetic-parasympathetic Balance.—Not a few investigators have maintained, on the basis of actual experience, that, in many cases, the existence of a sympathetic-parasympathetic imbalance and the character of this imbalance can be determined by pharmacodynamic methods. Others have denied this possibility by reason of the fact that certain individuals react strongly to both parasympathetic and sympathetic stimulants, and on the basis of the conflicting results obtained in pharmacodynamic studies. It cannot be denied, however, that, in general, individuals with exaggerated parasympathetic tonus react more strongly to parasympathetic, and individuals with exaggerated sympathetic tonus, to sympathetic stimulation than individuals with normal sympathetic-parasympathetic balance. Likewise, the effect of a given dose of a drug like atropin which paralyzes the parasympathetic nerves varies according to the functional state of the autonomic system, *i. e.*, a larger dose is required to abolish parasympathetic function in a vagotonic, and a smaller dose in a sympatheticotonic, than in a normal individual. Although it may not be possible, by means of pharmacodynamic methods, to detect very slight disturbances in the autonomic equilibrium in all cases, the results obtained by certain investigators (Danielopolu and Carniol, 1923; Lande, 1926; Simnitzky, 1927; and others) in the presence of disease associated with vagotonia or sympatheticotonia in general corroborate the clinical findings.

CHAPTER XIX.

THE AUTONOMIC NERVOUS SYSTEM IN DISEASE.

CLINICAL SIGNIFICANCE OF AUTONOMIC NERVOUS LESIONS.

OUR knowledge of the histopathology of the autonomic ganglia and ganglion cells, including the central autonomic centers, in relation to disease is as yet very meager. The data available at present show clearly, however, that many disease processes are associated with lesions of the autonomic nervous system (see Chapter XVI). In many instances, *e. g.*, in acute and chronic infectious diseases, the autonomic nervous lesions probably are due to the toxic effects of the disease. Nevertheless, they may play an important rôle in its progress, termination, and sequelæ. In other instances, lesions of the autonomic nervous system clearly constitute a causative factor in the disease. In certain diseases, *e. g.*, hyperthyroidism, Addison's disease, Raynaud's disease, etc., the dominant symptoms are directly referable to the functional condition of the autonomic nervous system.

Under experimental conditions, it has been shown that acute stimulation or depression of the autonomic ganglion cells may result in profound disturbances of visceral functions, although the cells in question have undergone no marked histological changes. Furthermore, these cells possess the capacity for recuperation in a remarkable degree; consequently, the histological picture of the autonomic ganglion cells during a disease process or following its termination does not, in all cases, afford a true index of the functional condition of the autonomic nerves during the course of the disease, whether of short or long duration. In the majority of the studies of pathological changes in autonomic ganglion cells hitherto recorded many minor changes in the internal structure of the cells have been disregarded. More intensive study of the cytological changes in the autonomic ganglion cells, particularly changes in the quantity and distribution of the chromidial substance and changes in the neurofibrillar apparatus, due to functional stimulation and depression, under rigidly controlled experimental conditions, probably will show that pathological changes in these cells are essentially indications of past or present functional disturbances, and that functional disturbances may also have existed *intra vitam* in ganglion cells which show no marked cytological changes.

Lesions of the autonomic ganglia and ganglion cells which arise during the course of certain diseases play an important rôle in the progress of the disease by reason of their stimulating or depressing effect on the vasomotor nerves. Depression of the vasomotor nerves results in a general fall in blood pressure and changes in the distribution of the blood in the organs; the supply in the splanchnic area being greatly increased while the central nervous system, skeletal muscles, and skin are relatively ischemic. Weins (1913) observed diminution in blood pressure in cases of malaria, not only during the attacks, but also during the intervening intervals, which he attributed to depression of the vasomotor nerves. Infectious diseases of children are not infrequently accompanied by sympathetic hyperexcitability. Severe acute intoxication in children is often accompanied by sympathetic hypotonus, which always indicates an unfavorable prognosis. The toxic effects of disease on the autonomic ganglion cells are also apparent in gastro-intestinal motility. Stimulation of the sympathetic or depression of the parasympathetic nerves results in constipation. On the contrary, depression of the sympathetic or stimulation of the parasympathetic nerves results in hypermotility of the gastro-intestinal musculature. Likewise, stimulation or depression of the secretory nerves, due to the toxic effects of disease on autonomic ganglion cells, may result in far-reaching glandular dysfunction.

Tuberculosis is not uncommonly accompanied by disturbances in the functional balance of the autonomic nervous system which play an important rôle in the dominant symptoms of the disease. As early as 1908, Laignel-Lavastine reported toxic lesions and atrophy of sympathetic ganglion cells and inflammation of the ganglia in the abdominal sympathetic plexuses in severe cases of tuberculosis. Later investigators, including Stämmeler (1923), also described pathological changes in the sympathetic ganglia in cases of tuberculosis. Stämmeler stated, however, that he never observed well-marked pathological changes in the sympathetic ganglia in uncomplicated cases of tuberculosis. In an extensive clinical study of tuberculous patients, Deutsch and Hoffmann (1913) found parasympathetic tonus predominant during the second stage and still more predominant during the third stage of the disease. The hectic flush so common in the later stages of tuberculosis, but which does not appear early in the disease, probably is an expression of parasympathetic hypertonus exaggerated during intervals of marked activity of the disease process. The relative slowness of the heart-beat often observed during periods of temperature, as compared with the heart-rate in other diseases during periods of the same degree of temperature also indicates exaggerated parasympathetic tonus. When the tuberculous process involves the intestinal tract, the discrepancy between the observed pulse-rate and that which

would be expected with the degree of temperature present is still greater. According to Pottenger (1917), an unusual slowing of the pulse-rate in the course of pulmonary tuberculosis, coincident with an increase in temperature of 1° or 2° F, should be regarded as cause to suspect a complicating intestinal tuberculosis.

The gastric hyperacidity which not uncommonly occurs relatively early in the course of tuberculous disease is also associated with exaggerated parasympathetic tonus. The patient's digestive powers may be above par at first, enabling him to utilize relatively large amounts of food. There is often increased gastro-intestinal motility associated with hyperacidity, which not infrequently results in nausea and a tendency to vomit. In some cases, exaggerated parasympathetic tonus also results in spastic constipation. These conditions, however, are not constant. During toxemia in pulmonary tuberculosis, as pointed out by Pottenger, sympathetic tonus is increased by reason of central stimulation and the reflex effect of the inflammation in the lung; consequently, sympathetic tonus may predominate. As soon as the acute toxemia subsides and central sympathetic stimulation is diminished or ceases, a condition of relative vagotonia again obtains in the majority of cases. The patient's appetite is improved and his digestive powers are increased. As a rule, the associated gastric hyperacidity is not sufficient to cause discomfort; sometimes it actually causes gastric distress. Digestion usually becomes impaired more and more and stasis and constipation become more pronounced as the disease advances and toxemia and depressive emotional states become more marked. The gastro-intestinal symptoms commonly observed during the later stages of tuberculosis are less suggestive of parasympathetic hypertonus than those usually observed earlier in the course of the disease. In those cases in which parasympathetic tonus clearly predominates during the later stages of the disease, it may, as Stämmeler (1923) suggested, be due to depression of the sympathetic tonus by reason of the toxic effects of mixed infection on the sympathetic ganglion cells.

On the basis of extensive histopathological studies, particularly those of Stämmeler (1923), it may be stated that arteriosclerosis is almost invariably associated with pathological changes in the autonomic ganglia. The clinical and experimental data available also indicate quite clearly that autonomic nervous lesions constitute a major factor in the causation of this disease. Arteriosclerotic lesions in man, like arterial lesions induced in animals by a wide variety of experimental procedures, are commonly accompanied by pathological changes in the autonomic ganglia and ganglion cells. The data obtained from experiments involving infection and toxic inflammation and those involving cholesterol feeding strongly suggest that lesions of the autonomic ganglia which probably result in

stimulation or depression of the autonomic ganglion cells play an important causative rôle in the arterial lesions (Stämmeler, 1923; Danisch, 1928; and others). Inasmuch as the arterial lesions induced experimentally in animals have much in common with arteriosclerotic lesions in man, the experimental data, in general, support the theory that pathological changes in the autonomic ganglia and ganglion cells constitute an important factor in the genesis of arteriosclerosis.

Muscular dystrophies have commonly been regarded as the result of lesions of the motor nerves supplying the muscles in question. Such probably is the case in most instances. This opinion has been accepted so generally that studies undertaken to determine the causes of muscular dystrophies rarely included a careful histological study of either the sympathetic ganglia or the preganglionic efferent neurons. The accounts of such studies speak mainly of changes in the anterior horn cells, disregarding the condition of the cells in the intermediolateral cell column.

Hitzig (1893) reported profound pathological changes in the right, and only slight changes in the left cervical sympathetic ganglia in a case of dystrophy of the muscles of the right upper arm. More recently, Kuré *et al.* (1925) reported fairly definite degenerative changes in the sympathetic trunks and the sympathetic fibers in the peripheral nerves in 2 cases of progressive muscular dystrophy. They also reported definite atrophic changes in the trapezius, deltoideus, and pectoralis major muscles in 6 out of 21 patients many months after cervical sympathectomy carried out for various therapeutic purposes. Muscle tissues obtained by biopsy, in these cases, revealed typical dystrophic changes in the muscles in question. The muscles of the upper arm were involved in some cases, but the muscles of the forearm and the small muscles of the hand showed no atrophic changes. Kuré (1927) advanced the opinion that the occurrence of muscular dystrophy in certain patients, following sympathectomy, and its non-occurrence in others may be correlated with the functional sympathetic-parasympathetic balance which obtains regarding the innervation of the muscles in each case. If sympathetic tonus predominates, the trophic innervation of the muscles is mainly sympathetic; consequently, sympathectomy results in muscular dystrophy. That parasympathetic denervation may also result in muscular dystrophy was reported by Imagawa (1927), who described dystrophic changes in the muscles of the tongue following section of the chorda tympani, and Sunaga (1927), who described similar changes in the eye muscles following extirpation of the ciliary ganglion.

On the basis of their clinical findings and the results of experimental studies involving careful histological examination of muscles deprived of their sympathetic or parasympathetic innervation for

relatively long periods, Kuré *et al.* advanced the opinion that progressive muscular dystrophy, as distinct from amyotrophic lateral sclerosis and spinal progressive muscle atrophy, is caused mainly by lesions of the autonomic nervous system. They also pointed out as significant for differential diagnosis, that the atrophic changes associated with amyotrophic lateral sclerosis, spinal progressive muscle atrophy, and neurotic muscle atrophy are most marked in the small muscles of the hands and feet and the muscles of the forearms and legs, whereas, progressive muscular dystrophy involves mainly the muscles of the face, shoulder girdle, arms, and thighs, leaving the small muscles of the hands and feet and the muscles of the forearms and legs relatively unaffected. The difference in the degree of involvement of these two groups of muscles, in progressive muscular dystrophy, is explained on the assumption, based on anatomical and physiological data, that the former are more abundantly supplied by autonomic nerve fibers than the latter. In view of the present status of our knowledge regarding the functional significance of the autonomic innervation of skeletal muscles, further investigation of progressive muscular dystrophy in relation to autonomic nervous lesions is highly desirable. If the findings of Kuré and his associates are confirmed by the results of further studies, they will be of far-reaching clinical and physiological importance.

THE AUTONOMIC SYSTEM IN ENDOCRIN DISORDERS.

Chronic Adrenal Insufficiency (Addison's Disease).—Chronic adrenal insufficiency, first described by Addison in 1855, is a relatively rare disease which usually develops in the third or fourth decade of life. It is characterized by adynamia, gastro-intestinal disturbances (constipation alternating with diarrhea), pigmentation of the skin and mucous membranes, and low blood pressure. Body temperature is often subnormal, particularly in the later stages of the disease.

Tuberculosis involving the adrenal glands has been found to be the most common cause of this disease. Simple atrophy, chronic interstitial inflammation resulting in atrophy, and malignant disease invading the adrenal capsules or restricting their blood supply by reason of pressure have also been recognized as causes of adrenal insufficiency. In a certain number of cases, the adrenal bodies themselves show no lesion, but adrenal hypofunction is brought about by pressure, inflammation or degenerative changes involving the coeliac ganglia.

While the symptom-complex associated with adrenal insufficiency rests on a subnormal output of adrenalin, some of the dominant manifestations of the disease, *e. g.*, the gastro-intestinal disorders

and low blood pressure, are directly referable to a functional imbalance of the autonomic nervous system. Not infrequently the dominant symptoms indicate general vagotonia.

Degenerative lesions involving the adrenals not only diminish the functional tissue, but also impair the secretory function of the nerve fibers supplying these glands; consequently, the remaining secretory tissue is deprived of its normal stimuli. Diminution of the adrenalin output in turn results in diminished sympathetic tonus, thus allowing parasympathetic tonus to gain the ascendancy. Low blood pressure, subnormal body temperature, and asthenia are essentially symptoms of parasympathetic hypertonus.

Certain of the older investigators also attempted to explain the excessive pigmentation of the skin, which occurs as an inconstant symptom of adrenal insufficiency, on the basis of disturbed autonomic function. Most of the data available at present do not support this theory. On the basis of a critical study of the anatomy and physiology of the pigmented portions of the skin, Bory (1926) advanced the opinion that the basal cells of the stratum germinativum act in close correlation with the adrenals and that, under certain physiological conditions, the skin either produces adrenalin or stimulates the adrenals to secrete. He regarded the excessive pigmentation of the skin, in adrenal insufficiency, as the result of overproduction of melanin by the skin in its attempt to compensate for adrenal hypofunction. The implied correlation between the skin and adrenals probably is brought about, at least in part, through the autonomic nervous system.

In those cases of adrenal insufficiency in which the adrenal glands are neither involved in the primary lesion nor exhibit evidence of pressure atrophy due to lesions of adjacent tissue, the primary cause of the disease must be sought in autonomic dysfunction. Not infrequently such cases reveal pathological changes in the coeliac plexus. Laignel-Lavastine (1924) recognized two types of the disease on the basis of etiology, viz.: (1) A type in which the primary lesion involves the adrenals, the autonomic system being involved secondarily; and (2) a type in which the adrenal insufficiency is the result of a lesion of the coeliac plexus. The symptoms of both types of the disease are very similar.

Danisch (1928) reported symptoms similar to those of adrenal insufficiency in man, viz.: emaciation, general weakness, and profound circulatory disturbances, in rabbits following extirpation of the coeliac ganglia. He also pointed out, however, that similar degenerative changes in the autonomic ganglia occur in various diseases in which there is no evidence of adrenal insufficiency. Many of the latter cases also exhibit profound circulatory and general secretory disturbances. On the basis of these considerations and his experimental findings, Danisch opposed the theory that lesions

of the autonomic system alone can give rise to the symptom-complex known as Addison's disease. He advanced the opinion that the full development of this symptom-complex depends mainly on dysfunction of the adrenal glands, including both the cortex and medulla, even though the primary cause of such dysfunction is a lesion of the autonomic nervous system.

Adrenal Hyperfunction.—On the basis of animal experimentation and pathological findings in man, it may be stated that hypersecretion of adrenalin is mainly the result of changes in the adrenal medulla. Hyperadrenalemia profoundly affects the autonomic nervous system, particularly the vasomotor nerves. In experimental animals, it results in death preceded by clonic muscular spasm, rapid respiration and vomiting. Postmortem examination reveals wide-spread hemorrhagic areas in the visceral organs and serous membranes, and necrotic areas, particularly in the liver and kidneys. These are essentially manifestations of increased blood pressure brought about by excessive stimulation of the vasomotor nerves. Continued moderate hyperadrenalemia, in experimental animals, gives rise to arteriosclerotic changes by reason of its stimulating effect on the vasomotor nerves (Danisch, 1928).

Neoplasms involving the adrenal medulla or other chromaffin bodies, in man, commonly result in a marked increase in blood pressure and early arteriosclerosis accompanied by profound metabolic disturbances and not infrequently apoplexy. Although the rôle of the autonomic nervous system in the symptom-complex associated with neoplasms of the chromaffin tissue has not been studied extensively, it may be assumed, on the basis of the results obtained in experimental hyperadrenalemia in animals, that these symptoms are mainly manifestations of sympathetic hyperstimulation due to excessive adrenalin in the circulation. Chromaffin tumors involving both adrenals may give rise to grave diabetes mellitus. That glycosuria can be produced experimentally by injection of adrenalin has long been known. This fact may be regarded as evidence that the hormone produced by one endocrin gland, may through its effect on the secretory nervous mechanism, bring about dysfunction of another endocrin gland. Diabetes resulting from chromaffin tumors probably is brought about through the inhibitory effect of adrenalin on the pancreatic islands.

Hyperthyroidism.—The functional relationship of the thyroid gland to the autonomic nervous system has been studied extensively. That this gland is subject to regulatory nervous influences is well known. On the other hand, it is also well known that the thyroid hormone exerts an influence on the functional balance of the autonomic nervous system. Data are not wanting which seem to support the neurogenic theory of hyperthyroidism. Not infrequently the symptoms of hyperthyroidism may be recognized in the absence

of any demonstrable lesion of the thyroid gland. In certain cases, it has also been possible to trace the cause of thyroid hyperactivity to a specific lesion of the cervical sympathetic. For example, Herzen reported a case of unilateral thyroid hyperactivity due to compression of the cervical sympathetic by a fractured clavicle. In this case, the symptoms of thyroid hyperactivity subsided following removal of the pressure by reduction of the fracture. Symptoms of hyperthyroidism brought about by stimulation of the thoracic sympathetic trunk have also been reported. That hyperthyroidism is frequently accompanied by pathological changes in the autonomic ganglia and ganglion cells has been determined by careful histopathological studies (Stämmeler, 1923; Mogilnizky, 1923; and others). There is also a degree of parallelism between the severity and duration of thyroid hyperactivity and the extent of the changes in the autonomic ganglion cells. Yet, there is at present no conclusive evidence that these changes play a rôle in the genesis of hyperthyroidism. They probably are to be regarded as a result and not as the cause of the disease. That they play an important rôle in the course, termination, and sequelæ of the disease cannot be doubted.

Although preëxisting functional disturbances and pathological lesions of the autonomic nervous system cannot be ruled out as etiological factors in hyperthyroidism, this condition probably arises as a primary disease of the thyroid gland in the majority of cases. Certain of its dominant symptoms, *e. g.*, tachycardia, exophthalmos, perspiration, and diminished gastric secretion, however, are directly referable to increased sympathetic stimulation by reason of the increased output of the thyroid hormone. Consequently, the autonomic nervous system plays an important rôle in the symptom-complex associated with hyperthyroidism, which cannot be disregarded in the treatment of the disease. Sympathetic hyperirritability resulting from the disease in turn reacts unfavorably on the thyroid gland.

Continuous stimulation of the thyroid, in certain cases, leads to its exhaustion and is followed by a condition resembling myxedema. The enlargement of the thyroid may subside, but the symptoms of sympathetic hyperstimulation continue. Adrenal hyperactivity probably plays a rôle in these cases, but the continued sympathetic hyperirritability, as the thyroid approaches exhaustion, can be explained without assuming hyperactivity on the part of the adrenals. In many cases of hyperthyroidism, particularly in the young, hyperplasia of the thymus also exists. Nothing is definitely known regarding the influence of the thymus on the autonomic nerves. It is not improbable, however, that hyperplasia of the thymus may be a factor in the symptomatology of thyroid disease.

Parathyroid Disease.—Vassale and Generali (1900) first called attention to a relationship between parathyroid extirpation and the symptoms of tetany which follow the removal of these glands in certain animals. Parathyroidectomy also gives rise to symptoms of tetany in man. Transplantation of parathyroids or injection of parathyroid extract ameliorates the symptoms and sometimes cures tetany. The metabolic disturbances following parathyroidectomy strongly suggest that the parathyroid hormone exerts an influence on the autonomic nervous system. According to certain investigators, it exerts an inhibitory influence on the sympathetic nerves and adrenals. Parathyroid tetany may be aborted in certain cases by extirpation of the adrenals. On the other hand, active symptoms may be brought on by injection of adrenalin in cases of latent tetany. The parathyroids also sustain an important functional relationship to the gonads. Parathyroidectomy is not followed by tetany in castrated animals. Furthermore, subsidence of the symptoms of tetany in parathyroidectomized animals, following castration, has been reported. The administration of parathyroid extract produces a fall in blood pressure in normal animals. Excessive or prolonged administration of this extract produces a very high calcium and phosphorus content in the blood serum and eventually results in convulsions and death. All these data indicate an intimate functional relationship between the parathyroid hormone and the autonomic nervous system.

Diseases of the Pituitary Body.—The pituitary body is a complex organ derived in part from the neural tube and in part from the alimentary canal. It produces more than a single hormone and subserves a variety of functions, some of which have no obvious relation to the autonomic nervous system. Experimental results tend to prove that the anterior lobe definitely affects the growth of the osseous system and the development and function of the genital organs. They also substantiate the theory that the posterior lobe (*pars nervosa* and *pars intermedia*) plays an important rôle in the regulatory control of metabolism and adiposity. The effect of pituitrin on the contraction of smooth muscle also supports the theory that the posterior lobe influences the function of all involuntary muscle. The anterior lobe probably exerts a similar effect on the voluntary muscles. Insufficiency of the anterior lobe is associated clinically with atonicity and weakness of the voluntary musculature.

Most of the foreign schools, particularly the French school headed by Camus and Roussy, support the theory that nearly all the disorders which have been attributed to pituitary dysfunction, such as changes in the osseous system, adiposity, diabetes insipidus, etc., are referable, not to lesions of the pituitary body, but to lesions of adjacent areas of the hypothalamus. This contention has not

been fully established. Neither has the theory that abnormal pituitary secretion, through its effect on the autonomic nervous system and various body tissues, gives rise to certain more or less definite syndromes been disproved. The relief of such disorders as polyuria and obesity, in certain cases, by the administration of the active principles of the lobes in question strongly suggests that these disorders have their origin in pituitary dysfunction. A direct influence of the anterior pituitary lobe in the development and regulation of the genital system has also been demonstrated experimentally. In the recent experiments of Smith and Engle (1927), transplantations of anterior pituitary tissue into sexually immature mice and rats rapidly induced precocious sexual maturity, as evidenced by the appearance of all the signs of sexual maturity in untreated animals maturing in the usual time. Anterior pituitary transplants in sexually mature animals also elicited marked reactions in the ovaries and other genital organs. The genital system of the immature male did not respond as rapidly to anterior pituitary transplantations as did the female system, but the effect of the treatment was unmistakable.

That the influence of the anterior pituitary lobe is exerted directly on the gonads and through them on the other genital organs was shown, in the experiments of Smith and Engle, by the ineffectiveness of anterior pituitary transplantations in spayed and castrated animals. These authors also showed that the effectiveness of anterior pituitary transplantations is not lessened by extirpation of the thyroid or adrenal glands, and that transplantations of endocrine glands other than the anterior lobe of the pituitary neither retard nor accelerate the development of the immature genital system.

Although certain effects of pituitary lesions have been amply demonstrated, disorders which have been referred to pituitary dysfunction have their origin in lesions of the hypothalamus. Furthermore, it is not improbable that pituitary dysfunction may, in certain cases, be referable to hypothalamic lesions.

Although the effect of pituitrin on smooth muscle is well known, we have no definite data regarding the rôle of nervous influences in producing this effect. Neither do the data available at present afford an adequate basis for any definite conclusions regarding the rôle of the autonomic system in disorders referable to the pituitary gland. In view of the present confused state of our knowledge regarding the exact functions of the pituitary body, and the character of the symptoms which have been referred to pituitary dysfunction, exact knowledge regarding the rôle of the autonomic system in pituitary disease awaits further investigation.

Disorders Referable to the Ovaries.—Our knowledge regarding the relation of the ovarian hormone to the autonomic nervous system has been greatly advanced during recent years, particularly

by the results of studies in metabolism during pregnancy, following parturition, and in the climacteric. That the ovary exerts an important regulatory influence on carbohydrate metabolism is now well known. The blood-sugar curve during pregnancy and parturition runs a very definite course. The sugar content of the blood is low at the close of pregnancy, rises abruptly during parturition and falls again before the end of the first week after parturition. Hyperglycemia antemenstrum has also been reported. This probably is to be regarded as the result of sympathetic stimulation. Disturbances in carbohydrate metabolism resulting in hyperglycemia have also been observed following castration.

The symptoms commonly associated with the menopause probably are the result of cessation of the ovarian function. These symptoms are highly variable and depend, in a large measure, on constitutional peculiarities of the individual. In addition to changes in metabolism which are expressed primarily in the common tendency to increased deposition of fat, the vasomotor changes most clearly indicate disturbances in the functional state of the autonomic nervous system.

The fact that sympathetic irritability is increased during the climacteric and following castration seems to indicate that the ovarian hormone exerts an inhibitory influence on the sympathetic nerves. Certain experimental data have an important bearing on this point. The injection of adrenalin, as is well known, commonly gives rise to glycosuria. This result can be prevented, however, by the simultaneous injection of ovarian extract. The removal of the sympathetic inhibitory influence of the ovarian hormone during the climacteric permits the sympathetic tonus to gain the ascendancy, resulting in marked vasomotor disturbances. The sudden hot flashes, so common during this period, probably are the result of the shifting of large volumes of blood from the splanchnic area toward the periphery by reason of sympathetic stimulation. This at once explains the flushing of the skin as well as the sensation of warmth. Adler also regards the severe headaches associated with the menopause as the result of hyperirritability of the cranial sympathetic nerves. On the other hand, certain symptoms associated with the menopause also suggest parasympathetic hyperirritability.

Disorders Referable to the Testes and Pineal Body.—Our limited knowledge of the functional relationships of the testes and pineal body to the autonomic nervous system rests mainly on anatomical and experimental data. That early castration results in eunuchoidism, and pineal neoplasms, in some cases, result in precocious sexual maturity is well known. These results probably do not depend on the direct effect of deprivation of the internal secretion of the gland in question. Some of the symptoms are referable to modified function of other endocrin organs by reason of the deprivation of

the hormone produced by the latter. The most striking effects of interstitial and pineal insufficiency involve metabolism and growth, and are expressed in the eunuchoid habitus in the one case, and early sexual maturity and development of the secondary sexual characters in the other. Both clinical and anatomical data show clearly that the pineal gland exerts a regulatory influence in the development of the genital organs, particularly the testes. In this regard, its influence seems to be antagonistic to that of the posterior lobe of the hypophysis, the destruction of which under experimental conditions, commonly results in genital atrophy. To what extent interstitial and pineal hormones affect the autonomic nervous system is not known. On the basis of the available data, it seems highly probable, however, that their regulatory influence in the control of visceral functions is brought about, at least in part, through the autonomic system. Exact knowledge in this field awaits further investigation.

EMOTIONAL DISTURBANCES OF VISCERAL FUNCTIONS.

Visceral Manifestations of Emotional Stress.—The existence of an intimate relationship between the visceral functions and the emotions is a fact of common experience. In general, pleasurable emotions promote and painful or disagreeable emotions depress the visceral functions. Strong emotional excitement invariably results in an immediate discharge of nervous impulses through the autonomic nervous system. The immediate reactions evoked tend in general to produce functional responses which are beneficial to the individual. For example, there may be a discharge of adrenalin into the blood stream with consequent changes in the blood flow, or blood sugar may be mobilized for the possibilities of extreme muscular exertion. Izquierdo and Cannon (1928) recently reported that emotional excitement lasting one minute, in experimental animals (cats), is followed quickly by a marked rise in the number of red corpuscles in the blood. The maximal increase occurred immediately after the minute of excitement; within one-half hour the number of red cells had returned to normal. Emotional polycythemia failed to occur, in their experiments, following extirpation of the upper abdominal sympathetic trunks and section of the splanchnic nerves. Menkin (1928) reported that emotional excitement for ten to fifteen minutes, in normal cats, also resulted in a relative increase in mononuclear leukocytes, which was maintained for a period of ten to fifteen minutes following the period of excitement; within one-half hour the number of mononuclear leukocytes had returned to the former level. Emotional excitement of sympathectomized animals for ten to fifteen minutes, in his experiments, resulted in no immediate changes in the relative number of mono-

nuclear leukocytes. Menkin advanced the opinion that sympathetic stimulation by reason of emotional excitement results in splenic contractions which force into the circulation an increased number of both erythrocytes and mononuclear leukocytes. These findings probably explain the emotional leukocytosis sometimes reported in patients while in a state of fear or apprehension preceding an operation.

Emotional excitement also exerts an influence on the basal metabolic-rate. In a series of experiments on hypnotized persons, Grafe and Mayer (1923) found that the metabolic-rate could be profoundly altered, in certain individuals, by the suggestion of various calamities, *e. g.*, death of relatives, amputation of limbs, etc. In 9 such tests, the metabolic-rate was increased 5 to 25 per cent. In 4 experiments no change or only a slight lowering of the metabolic-rate was observed. In experiments made on psychasthenic war veterans, Ziegler and Levine (1925) found a marked rise in the metabolic-rate as the result of emotional excitement in 11 cases, a slight fall in 3, and no change in 1 case. As reported by Landis (1925), anticipation of strong electrical stimulation caused a rise of 6, 17, and 37 per cent respectively in the metabolic-rate in 3 persons tested. In studying the effect of the knowledge of an impending operation on the basal metabolic-rate in three groups of patients, *viz.*: (1) patients with nervous stability and a normal metabolic-rate, (2) patients with hyperthyroidism who had received iodine according to present-day preoperative routine, and (3) patients with hyperthyroidism who had not received iodine therapy, Segal, Binswanger, and Strouse (1928) observed no marked change in the metabolic-rate on the day of operation in the first two groups, but a marked rise in the metabolic-rate was observed in the third group of patients on the morning of the supposed operation.

The effect of the emotions on the digestive functions is most striking. Cannon (1911) described instances of complete inhibition not only of gastro-intestinal motility, but also of the secretory activity of the digestive glands in consequence of emotional stress. Persistent worry not infrequently results in indigestion. Fear may inhibit salivary, gastric and pancreatic secretion. Likewise, the entire digestive process may be profoundly disturbed by anxiety or distress. On the basis of a recent study of the psychic and emotional factors in disorders of the digestive tract, McLester (1927) estimated that one-third of the patients with digestive disorders have no recognizable organic disease, but are suffering because of lack of emotional balance. Cabot (1925) reported a case in which failure of a fracture of the leg to unite was found to be due to impaired nutrition resulting from worry. The patient, being fearful lest his family was suffering because of his absence from home, had no desire for food (inhibition of hunger contractions of the stomach). Failure to take food resulted in impaired nutrition which in turn

resulted in such impairment of the reparative processes that the fractured bone failed to unite. Assurance that his family was being cared for and was well and happy brought about immediate improvement in the patient's condition; he ceased worrying and began to eat heartily. As his nutritive condition improved, his broken bones also began to knit.

Instances of digestive disorders due to emotional stress could be multiplied indefinitely. Emotional excitement does not result in comparable digestive disorders in all persons. The gastro-intestinal reaction to an emotion depends in a large measure on the functional condition of the autonomic nervous system, the endocrin glands, and the acid-base balance. According to Lueders (1928), "the gastro-intestinal reaction to an emotion persists only as long as the original object causing the emotion is present; in other words, the visceral expression of an emotion ceases when the emotion is changed to an abnormal syndrome or mood." The normal autonomic nervous system tends to maintain normal gastro-intestinal function, even though a dominant emotionalism has become habitual following the removal of the cause of the emotional reaction. According to Lueders, many patients with psychoses exhibit normal or increased gastro-intestinal function. He usually found no depression of gastro-intestinal motility or secretory activity in psychoses, except when associated with somatic disorders, or when the patient exhibited sympatheticotonia or some atonic condition of the autonomic system. According to his findings, gastro-intestinal function is increased in psychotic patients of the vagotonic type.

In most cases of impaired digestion due to emotional excitement, the symptoms referable to the digestive organs are caused by inhibition of gastro-intestinal motility and secretion of the gastric juices by reason of sympathetic stimulation. Gastro-intestinal hyperactivity due to emotional stress, though not unknown, is less common and, in most cases, less persistent. In these cases the symptoms may be caused either by sympathetic inhibition or parasympathetic stimulation.

The sympathetic nerves supplying the heart and blood vessels, unlike those supplying the digestive tube, convey not inhibitory, but excitatory impulses. Consequently, the excitement which inhibits the digestive processes results in increased heart-rate and rise in blood pressure. The increased pressure is produced by the force propelling the blood into the arteries and the resistance to the outflow from them. Since sympathetic impulses both accelerate the heart-rate and constrict the arterioles, they bring about increased blood pressure by affecting both factors positively. The effect of even moderate excitement on blood pressure is unmistakable. According to Gallavardin and Haour (1912), the slight excitation incident to taking the blood pressure is, in many cases, sufficient

to cause a rise of 25 to 35 mm. in the systolic level. In their experience, the first systolic reading was usually higher than those taken later in the same subject. Schrumpf (1910) reported a case in which fear of a serious diagnosis caused a rise in blood pressure of 33 per cent. When reassurance was given, the blood pressure promptly returned to normal. Fright, anger, or pleasure, in extreme cases, may cause a rise of 90 mm. of mercury (Cannon, 1928).

During the World War, cases of so-called "soldier's heart" were not uncommon. In these cases, the slightest excitement or emotional stress usually resulted in a marked increase in the pulse-rate (130 to 150 beats per minute). The emotional stress incident to the war had resulted in such sensitization of the sympathetic control of the heart, in these patients, that even mild stimulation produced extreme effects (Cohn, 1919).

That emotional disturbances tend to increase the output of sugar in diabetic patients has long been noted. In many of these patients, the degree of diabetes exhibited tends to vary in response to nervous and emotional influences. Emotional disturbances are not infrequently accompanied by low sugar tolerance and actual hyperglycemia even in the absence of diabetes. On the basis of quantitative determinations of the blood sugar in students before and after participation in intercollegiate athletic contests and scholastic examinations, Cannon (1915) pointed out that emotional disturbances also exert a strong influence tending to bring about hyperglycemia in normal individuals. Inasmuch as the blood sugar is readily increased by sympathetic stimulation, it may be assumed that this influence of emotional stress is exerted through the sympathetic system. Although it is not clear that diabetes can be initiated through such sympathetic stimulation alone, the available data show clearly that any existing diabetes may be aggravated by emotional stress.

Emotional disturbances may also profoundly affect the visceral organs through influences on the thyroid gland. Maranon (1921) reported an extensive series of cases of hyperthyroidism brought on by emotional stress during the World War. That psychic and emotional disturbances are important etiological factors in hyperthyroidism, in many cases, is a fact of common clinical observation. Furthermore, any severe or unaccustomed shock to the emotional make-up of the patient may aggravate the symptoms in a mild case and convert it into a severe one. Latent or potential cases of hyperthyroidism may be transformed into active cases by varying degrees of nervous shock. That sympathetic stimulation plays an important rôle in these cases cannot be doubted. It probably is a factor in producing the increased thyroid hyperactivity. The dominant symptoms associated with the disease also suggest the existence of autonomic functional imbalance.

Many other visceral disorders brought about by the effect of psychic and emotional disturbances exerted through the autonomic nervous system might be mentioned, *e. g.*, disorders of menstruation, secretion of milk, emptying of the bladder, perspiration, etc. Indeed, perhaps every visceral function is subject to influences exerted by psychic and emotional states through the autonomic nervous system.

The reactions of the visceral organs to an emotion may be regarded as the visceral contribution to the complete emotional state. Impulses emanating from the central autonomic centers in response to emotional stimulation, result in the excessive discharge of adrenalin and other hormones into the blood stream, and the liberation of sugar to such an extent as to cause transient glycosuria. Energy is thus supplied for the muscular exertion which may be called for in possible physical combat or flight, particularly in emotions like fear, anger, or rage. Under existing social conditions, this autonomic defensive mechanism is, in a large measure, held in restraint. It has been assumed by some (Lueders, 1928) that repeated activation of this mechanism, if unsatisfied by instinctive expression, may result in an irascible or a fearsome disposition. Thus, the visceral reactions to emotional stimuli, particularly in individuals with an unstable or hyperirritable autonomic system, would contribute to the causes of affective disorders. Cannon and his associates have shown, however, that the discharge of adrenalin is increased by muscular activity. The visceral concomitants of emotional excitement also persist for some time after the stimulus has ceased to act. On the basis of results obtained in animal experiments, Cannon and Britton (1927) attributed this to the continued discharge of adrenalin due to the emotional excitement and its expression, and emphasized the importance of limiting the expression of strong emotions, such as fear and rage, in order to avoid a persistent state of disquiet.

That somatic and visceral disorders and diseases may initiate subjective emotional reactions is generally conceded. In view of the important rôle of the autonomic nervous system in visceral disorders, it is reasonable to assume that, under certain conditions, autonomic dysfunction may precipitate or maintain abnormal affectivity. On the basis of an extensive study of gastro-intestinal reactions to emotions in patients with psychoses, Lueders (1928) advanced the opinion that protracted chronic emotionalism and morbid moods affect the visceral functions less and less, but exert their greatest damaging influence at higher levels. Consequently, the mental and moral faculties become impaired and dominated by uncontrolled emotionalism, obsessions, hallucinations, etc. Similar opinions have also been advanced by other investigators. On the basis of a study of 600 patients with psychoses, Claude (1925) concluded that "the intensity and rapidity of the morbid periods

in the psychoses seem to be proportionate to the excitability of the vegetative system, probably through the intermediation of the humoral or endocrin mechanism. It is not astonishing, therefore, if a characteristic state of the neurovegetative system is to be found constantly in the organic symptomatology of certain psychoses." In view of all the data available, psychoses cannot be regarded as merely abnormal functioning of the brain or central nervous system, but represent changes in the entire individual. Even under normal physiological conditions, it may be assumed that the mind is influenced by the entire body. Consequently, psychical processes are not limited to the cerebral cortex. Affective behavior must be regarded as a function of the whole organism. The emotional life of the individual is determined in a large measure by the functional reactivity and balance of the autonomic nervous system.

Neurological Basis of Emotional Visceral Disorders.—The effects of the emotions on the visceral organs are just as real as the effects produced by the contraction of voluntary muscles in response to cortical impulses, although the level of the nervous control of the former is subcortical and purely involuntary. That decorticated animals (cats and dogs) are capable of displaying a type of behavior which is commonly regarded as expressive of emotional excitement is well known. In a recent experimental study, Bard (1928) demonstrated that the remarkable activity, best described as sham rage, which may be evoked in the cat almost immediately after decortication, is dependent on the integrity of a definite part of the diencephalon, but fails to develop following ablation of the caudal half of the diencephalon. By combining the results observed following transverse sections of the brain stem with those observed following ablation of the dorsal portion of the diencephalon, he was able to determine that the discharge of nervous impulses which brings about the motor manifestations of sham rage is mediated through neural mechanisms which lie within the caudal half of the hypothalamus and the most ventral and most caudal portions of the thalamus.

The quasi-emotional behavior of the decorticated animal closely resembles the behavior of the infuriated normal animal. It involves both somatic and visceral activities. The latter are clearly due to impulses mediated through the autonomic nervous system. The existence of autonomic centers in the ventral portion of the diencephalon is amply demonstrated (see Chapter III). These are the highest known centers for the regulatory control of the visceral functions. In the light of Bard's findings, it may be assumed that the influence of emotional states on the visceral functions is mediated through these centers. This view is also supported by other experimental and clinical data. In view of all the data available,

it may be assumed that impulses emanating from these diencephalic centers, in response to the stimulus of emotional excitation, are discharged downward and outward to the viscera and muscles to produce the visceral and somatic manifestations of emotional excitement, and also upward to the cortex.

In general, the numerous and complicated reflexes which determine somatic and visceral states, *e. g.*, bodily posture, gastro-intestinal tonus, etc., do not affect consciousness. Likewise, the neural mechanisms for the primitive emotions probably are not associated with consciousness. Reactions carried out by purely subcortical mechanisms may, however, under certain conditions, break into the realm of consciousness and call forth cortical reactions. Some of the most characteristic features of emotional experience probably can be explained on this basis.

Although the thalamic, like other subcortical neural mechanisms, are subject to inhibitory influences emanating from the cortex, they are, in a large measure, capable of independent activity in conformity with certain definite reaction patterns. This activity plays an important rôle in all involuntary control of somatic and visceral functions, such as bodily posture, facial expression, gastro-intestinal tonus, etc. During emotional stress, the thalamic mechanisms involved are relatively free from cortical control; consequently, their influence in both somatic and visceral functions is exaggerated. In the somatic realm, this results in the postures and facial expressions characteristic of the various emotions. In the visceral realm it results in varying degrees of functional disturbance, depending, in a large measure, on the nervous constitution of the individual. These functional disturbances, under normal conditions, constitute an essential part of the emotional picture, but they become exaggerated, in many instances, to the point of positive visceral disorders.

In view of the above considerations, it must be apparent that emotional reactions exhibit many of the characteristics of reflex responses. Reflexes are elicited by appropriate stimuli. For example, food in the mouth calls forth a flow of saliva, irritation of the mucosa of the respiratory passages provokes coughing, etc. Likewise, emotional expressions are called forth by certain definite stimuli. Watson (1925) has shown that loud sounds and indications of loss of support are the natural stimuli for the reaction of fear in infants from the beginning. Likewise, limiting or hampering the freedom of bodily movements in infants is a natural stimulus to rage.

Under experimental conditions and as a result of training, reflexes can be called forth by agents other than their natural stimuli, if only they are closely associated in time with the latter. For example, if a bell is rung repeatedly at the same time that food is placed in the mouth, the ringing of the bell alone will call forth a

flow of saliva. In like manner, all sorts of ordinarily indifferent agents, indeed anything that will stimulate a sense organ, may become effective agents in calling forth reflex responses by close association in time with the normally effective stimuli. Reflexes called forth in this manner are called conditioned reflexes. Conditioned reflexes, as shown particularly by the exhaustive studies of Pavlov (1927), play an enormous rôle in our ordinary behavior and enrich experience by constantly giving new significance, for individual reactions, to objects and events in the world about us.

Our emotional reflexes also become complicated by the conditioning of indifferent stimuli. For example, the baby has no fear of a doll when presented, but expresses a desire to play with it. Now if the doll is presented repeatedly, but at the same time a loud sound is made, the baby manifests fear; the doll has become the conditioned stimulus for the fear reaction evoked by the loud sound. Thereafter, the baby manifests fear whenever the doll is presented, even though no sound is heard; the doll has become the symbol of a natural stimulus to fear. In ways similar to this, indifferent circumstances of an emotional disturbance may become effective stimuli for renewal of the disturbance, particularly in individuals with unstable emotional balance.

The individual with a stable and well-disciplined nervous system is able, in a large measure, to suppress the outward expressions of emotion. Nor does he respond to conditioned emotional stimuli, or at least not in the same degree as to the normal stimulus. His visceral responses to emotional influences may be intense momentarily, but they do not usually result in serious visceral disorders. Persistent disorders of visceral functions due to emotional disturbances occur most commonly in association with psychic or nervous instability. They are none the less real, however, and, since they are mediated through the autonomic nervous system, they are not subject to direct cortical influence, and persist as long as the autonomic hyperstimulation prevails. It must, therefore, be regarded as futile to treat the visceral symptoms without reference to the emotional cause. On the other hand, if the patient can be restored to emotional equilibrium, the visceral disorders of emotional origin soon subside.

THE SPLANCHNOPERIPHERAL BALANCE IN INFECTIOUS DISEASES.

Nervous Regulation of Leukocyte Distribution and Permeability of Blood Vessels.—That the leukocytes play an important rôle in all the local reactions connected with infection and inflammation has long been known. The early experiments of Goldscheider and Jacob (1894) also showed that marked changes in the number of

leukocytes in the peripheral blood may take place almost instantaneously. In their experiments, the injection of a peptone solution into the circulation was followed immediately by a sharp drop in the number of leukocytes throughout the peripheral area. The ingestion of food is usually followed by a slight increase in the number of leukocytes in the peripheral blood. Widál and his associates (1920) observed a decrease in the number of leukocytes in the peripheral vessels in certain patients after taking milk into the empty stomach. Comparative studies also showed that while there was a decrease in the number of leukocytes in the peripheral blood, there was an increase in the splanchnic vessels, and *vice versa*. Müller (1922) found that the injection of non-specific albumen preparations, minute amounts of salt solution, distilled water, or air also produced an immediate leukopenia throughout the peripheral area. The leukopenia produced by injection of albumen lasted thirty minutes, and that produced by injection of physiological salt solutions and air lasted five to ten minutes. More recently Müller and Myers (1924) found the peripheral blood almost devoid of leukocytes for about ten minutes following the injection of 10 cc. of a 20 per cent solution of peptone. During this period the leukocytes were concentrated in the vessels which are innervated by the splanchnic nerves, particularly those of the liver.

The peripheral leukopenia produced by the injection of solutions of peptone, non-specific albumen, etc., involves only the polymorphonuclear leukocytes, and is apparent throughout the entire peripheral area. If one limb is deprived of its sympathetic innervation, blood taken from this limb, following injection of one of the above solutions shows no marked reduction in the number of leukocytes, although the rest of the peripheral area exhibits leukopenia. This fact strongly supports the theory that the distribution of leukocytes is regulated through the autonomic nervous system.

Data obtained by Müller (1926) in two cases of insulin shock in diabetic patients indicate that while the peripheral vessels are dilated by reason of parasympathetic overstimulation, the number of leukocytes in the peripheral blood is markedly increased. The watery perspiration produced during this interval also indicates that parasympathetic hypertonus increases endothelial permeability. In these cases, the leukocytes in the peripheral blood reached 19,000 and 28,000 respectively in less than fifteen minutes, and dropped to 7000, the level which obtained before insulin treatment, in less than ten minutes, following the administration of glucose by mouth. Simultaneously with the decrease of leukocytes in the peripheral blood, the alarming symptoms produced by parasympathetic hyperstimulation at the periphery subsided, thus showing that, under these conditions, the leukocyte curve runs parallel with the parasympathetic overbalance at the periphery. In a further

experimental study, Müller was able to show that parasympathetic hypertonus at the periphery is accompanied by sympathetic hypertonus in the splanchnic region. These data not only support the theory that the distribution of leukocytes is regulated through the autonomic nervous system, but also indicate that endothelial permeability is modified by autonomic nervous influences.

On the basis of the data set forth above and the results of further experimental studies, Müller advanced the following conclusions: "The number of leukocytes found in any vascular region of the body depends on the balance of the involuntary nervous system in this particular region. The leukocytes will be evenly distributed so long as the involuntary nervous system, vasodilators and vasoconstrictors, are in normal balance. The uniform distribution changes immediately if there is an overbalance in either direction. Such an overbalance never takes place in the entire body. If large areas are involved peripheral and splanchnic regions balance each other. An overbalance of the sympathetic, vasoconstricting portion causes local leukopenia, while overbalance of the parasympathetic, vasodilating part causes leukocytoses. Nervous action is always the primary cause of leukocytic activity as far as accumulation and decrease are concerned, even though the leukocytes are in no way directly connected with either the walls of the vessels or with the vasocontrolling nerves of the involuntary nervous system."

In a recent study of the white cell changes under a variety of conditions (infection, vigorous exercise, pregnancy, diabetic acidosis, etc.), Hoff (1928) found not only that the distribution of leukocytes is subject to nervous regulation, but also that the variation in the blood picture are closely correlated with other manifestations of changes in the functional balance of the autonomic nervous system, particularly variations in the acid-base balance. He also maintained that the output of myelocytes by the bone marrow is increased by experimental sympathetic stimulation, while vagus stimulation results in relative lymphocytosis.

Splanchnoperipheral Vasomotor Balance During Chill and Fever.—In a recent clinical and experimental study, Petersen and Müller (1927) found that the functional balance of the splanchnic and peripheral autonomic mechanisms also plays an important rôle in the symptoms of infectious diseases, particularly the chill and fever. Examination of the skin of a patient in a chill reveals pallor, pilomotor stimulation, transient perspiration and lowered temperature. The arterioles and capillaries are contracted. The muscles exhibit tremor which varies greatly in intensity. These phenomena cannot be explained as the direct effect of the bacteria or the toxin produced by them on the peripheral tissue, but must be regarded as secondary effects of the toxic agent mediated through the nervous system.

The results of Schottmüller's (1911) studies have shown that the chill is associated with the invasion of the blood stream by bacteria. He found that the chill was not caused by the mere presence of bacteria in the blood, but takes place some time after the invasion (thirty to ninety minutes, depending on the individual and the type and number of organisms), viz.: when the organisms or their toxic products have made contact with the body cells.

Müller and Petersen (1926) showed that the injection of bacteria, like the injection of peptone, salts, etc., results in profound alteration in the tonus of the blood vessels in both the peripheral and splanchnic areas, the splanchnic vessels being dilated and the peripheral vessels constricted. These diametrically opposite effects can hardly be due to the direct influence of the same toxic agent on the vascular endothelium or the neurovascular elements in both regions. More probably, the tonic state of the blood vessels is determined by the effect of the toxic agent on the nervous system, the splanchnic vessels being dilated in response to parasympathetic stimulation in that region, and the peripheral vessels constricted in response to sympathetic stimulation in the peripheral region. That there is increased parasympathetic activity in the splanchnic region during the interval of splanchnic vasodilatation is also indicated by the increased production of lymph with the onset of the chill. That this lymph arises in the splanchnic region is indicated by its high protein-content (Petersen *et al.*, 1923).

Petersen and Müller (1927) also pointed out that shock following perforation, acute pancreatitis, acute peritonitis, indeed every insult to the peritoneum, such as ordinary laparotomy, etc., leads to an alteration in the splanchnoperipheral autonomic balance with a redistribution of leukocytes resulting in splanchnic leukocytoses. In the case of perforation, the peripheral sympathetic and splanchnic parasympathetic orientation¹ is so pronounced that the peculiar "facies" may be regarded as more or less pathognomonic. Splanchnic parasympathetic orientation is most pronounced, according to their observations.

In a recent study involving changes in the splanchnoperipheral balance, Arquín (1928) pointed out a definite time relationship between altered tonus of the stomach and alteration in the peripheral leukocyte count. When the gastric musculature is actually contracting, the peripheral leukocyte count is increased; during periods of gastric dilatation the peripheral blood exhibits relative leukopenia. On the basis of this finding, he suggested that in

¹ Parasympathetic orientation, as used by Petersen and Müller, is not restricted to the functional state induced by stimulation of the parasympathetic nerves alone, but indicates the functional state of organs in a region in which metabolism, permeability, blood supply, action currents, etc., are increased. Sympathetic orientation, as used by these authors, denotes the converse condition, viz.: tissue rest.

certain pathological conditions which involve chronic gastric congestion and delayed digestion, one should expect prolonged gastric dilatation to meet the physiological digestive requirements, and consequently a prolonged peripheral leukopenia.

The findings of Müller and Petersen regarding the rôle of the autonomic nervous system in the distribution of the blood volume in the peripheral and splanchnic regions is somewhat at variance with the so-called Dastre-Morat law, according to which the concentration of the blood in the splanchnic region by reason of paralysis of the splanchnic vasomotor mechanism, as has been assumed to occur in shock, is balanced by emptying of the peripheral blood vessels. They have pointed out that when a limb is deprived of its vasomotor innervation by sympathectomy, its blood supply is not depleted, during shock, by drainage into the splanchnic region. They have also pointed out that the chill is not accompanied by paralysis in the splanchnic region, but, on the contrary, by profound stimulation. The splanchno-peripheral balance has become "fixed," with the splanchnic and peripheral region oppositely oriented. The effect of such fixation becomes apparent in the change in body temperature coincident with the onset of rigor or following it.

Contrary to the current teaching, they do not admit that heat production by reason of muscle tremor, plays any part in the increase in body temperature. The production of heat is naturally associated with an increased metabolic-rate, indicating increased activity of the splanchnic organs, particularly the liver. According to Petersen and Müller (1927), all the measurable functions of the liver are accelerated during the chill. They found the output of bile and bile pigments measurably increased both in patients and experimental animals. The reticulo-endothelium of the liver also takes up fat from the blood in one-half the time normally required (Jaffe, 1927). Increased permeability of the capillaries and liver cells associated with this increased activity is evidenced by the fact that hemoglobin injected into the blood stream during shock passes into the lymph at an increased rate, and that bile pigments also enter the lymph stream.

In further support of the theory that muscular tremor plays no part in the production of heat during the chill, and that the rise in body temperature is due to heat generated by reason of increased activity of the splanchnic organs, they advanced the results of animal experiments in which a condition approximating the normal human chill was produced by the injection of suspensions of living *B. coli*. Muscle and rectal temperatures were recorded both by means of clinical thermometers and delicate thermocouples. Constant leukocyte counts and observations on the lymph were also made. In no case in which an actual chill was produced did they observe an increase in muscle temperature, although there was a

sharp rise in the rectal temperature during the same interval. A comparable, but greater, increase in temperature was noted in the liver. Not infrequently an actual reduction in muscle temperature took place during the rigor while the rectal temperature was rising. This occurred even when there was no actual increase in the rate of heat loss at the periphery. An abrupt rise in the temperature of the muscles was observed only at the end of the chill, usually when a coincident increase in the number of leukocytes in the peripheral blood indicated some vasodilatation in the peripheral region. On the basis of these results, Petersen and Müller concluded that no increase in the production of heat takes place with the shortening of the muscle during rigor, and that delay in the warming of the muscles despite a rise in the temperature of the rest of the body, must be due to an autonomic fixation in the muscles which prevents the dilatation of the arterioles and capillaries.

The results obtained by the above authors seem to indicate that profound alteration exists in the splanchnic and peripheral organs during the chill, brought about by the effects of a toxic agent on the nervous system which are manifested through the autonomic nerves. The splanchnic organs are hyperactive, while the peripheral organs are relatively inactive. Peripheral vasoconstriction reduces the loss of heat from the skin. That this condition depends on sympathetic tonus is well known. The work of Petersen and Müller seems to indicate that a similar condition prevails in the skeletal musculature during the chill. On this basis, the skin, muscles, and peripheral blood vessels may be regarded as a unit in their responses to the altered conditions of the body. Muscle tremor may, therefore, be regarded as indicative of increased splanchnic activity and the production of heat in the splanchnic organs. Conversely, increased splanchnic activity may produce muscle tremor. If the increase in temperature takes place gradually, without the intense autonomic fixation apparent in chill, the tremor may not appear. This probably explains why ordinary fever is usually not accompanied by chill.

NERVOUS REGULATION OF IMMUNE REACTIONS.

The data set forth above regarding the autonomic nervous influences in the distribution of leukocytes and the permeability of the vascular endothelium strongly suggest that immunity and bodily resistance are, in a large measure, determined by the functional condition of the autonomic nervous system. The results of recent experimental studies have also shown that specific immune reactions are subject to nervous influences and that they may be initiated by specific reflex stimulation. In a series of experiments reported by Reitler (1924), the formation of antibodies was initiated,

in rabbits, by injection of an antigen into the ear following ligation of its vessels. The ear was also amputated immediately (about three seconds) after the injection. This result shows clearly that the formation of antibodies may be initiated reflexly and that it may occur in the absence of antigen in the circulating blood. Bogendorfer (1927) reported the results of a series of experiments, carried out on dogs, in which he was able to show that the production of agglutinin is influenced by impulses emanating from a central nervous center. The injection of a specific antigen which resulted in active agglutinin production in normal animals was without effect, in his experiments, in animals in which the spinal cord was previously transected in the cervical region. If the cervical spinal cord was transected after the production of agglutinin was initiated, however, following injection of the antigen, the reaction continued. Transection of the spinal cord below the cervical region did not prevent the initiation of agglutinin production in response to the injection of antigen. In a later series of experiments, Bogendorfer (1928) was able to show that the nervous control of agglutinin production is mediated through the sympathetic nerves, since it can be definitely inhibited or even prevented entirely by the administration, before injection of the antigen, of drugs which paralyze the sympathetic nerves. In his experiments, the administration of ergotamin in appropriate dosage, before injection of the antigen, effectively prevented agglutination, but when the drug was administered in the same dosage after the production of agglutinin was initiated, the agglutination reaction was not appreciably inhibited.

In so far as the results of these experiments demonstrate a nervous influence in the control of immune reactions, they support the theory advanced by Pfeiffer that the production of immune bodies represents a specific reflex secretory reaction to a specific stimulus. They also show that an immune reaction once initiated may continue in the absence of influences emanating from the nervous system. The effector apparatus involved in the nervous control of immune reactions is as yet unknown.

THE AUTONOMIC SYSTEM IN CARDIOVASCULAR DISEASE.

Nervous Factors in Abnormal Blood Pressure.—Blood pressure and the supply of blood to the tissues depend mainly on the caliber of the blood vessels and the force and rate of the heart-beats. Both these factors are regulated through the autonomic nervous system. Under normal conditions, an increase in blood pressure elicits reflex cardiac inhibition, tending to restore normal pressure. Under certain pathological conditions involving high blood pressure, the pressure may remain abnormally high, and even mount still higher,

although the heart is failing and the pulse weak. In attempts to explain this phenomenon, it has been suggested that the heart fails by reason of the high blood pressure. If such were the case, lowering of the pressure would relieve the heart, which, however, it fails to do. It has also been suggested that as the output of the heart diminishes, the tonus of the blood vessels is increased, thus decreasing the size of the vascular bed to be filled. If this reaction actually took place it might account for the maintenance of blood pressure at the normal level, but not for a further increase in blood pressure while the heart is failing. As is well known, one of the most powerful stimuli to the contraction of a muscle is its previous stretching. The profound disturbance of cardiac rhythm resulting from pericardial effusion probably is due in a large measure to interference with diastolic filling, and, therefore, with the stretching of the cardiac muscle. The marked hypertrophy of the left ventricle in aortic regurgitation, doubtless, is the direct result of increased work. The stimulus for such increased work probably results mainly from the increased stretching of the muscle due to the filling of the ventricle both from the atrium and the aorta. In like manner, the diastolic stretching of the cardiac musculature, due to raising the blood pressure by stimulation of the vasoconstrictor nerves, in attempts to stimulate a flagging heart probably is an important factor in bringing about the desired cardiac response. If the myocardium is diseased and the overstretched muscle fails to respond, such treatment must result in increased dilatation.

The work accomplished by the heart, even under normal conditions, is relatively enormous. Pope calculated that if, under conditions of normal blood pressure, the output of the heart were only 2.5 ounces (usually it is more) at each contraction, this would amount to 7.5 tons of blood per day. The work accomplished would be equivalent to lifting a ton of blood 122 feet. In view of these figures, it must be apparent that any increase in blood pressure adds materially to the amount of work required of the cardiac musculature; consequently, anything which tends to maintain the blood pressure at an abnormally high level, tends to deplete the cardiac reserve. The increased blood pressure associated with advancing age not uncommonly plays an important rôle in shortening the remaining span of life by reason of the increased work required of the heart. Nevertheless, the rise in blood pressure must be regarded as a necessary conservative measure. Attempts to lower blood pressure by means of vasodilator drugs, without attacking the cause of the rise, must, therefore, be fraught with some degree of danger.

Hypertension is not uncommonly associated with structural vascular lesions. It often occurs in the absence of such lesions, however, as a result of sympathetic stimulation. The cause of

such sympathetic stimulation is sometimes traceable to hygienic or dietetic variations, sometimes to acute or chronic disease processes, and not infrequently to psychic and emotional disturbances.

Hypotension is often more urgently dangerous than hypertension. The rôle of adrenalin deficiency in abnormally low blood pressure is well known, particularly in Addison's disease. Adrenalin deficiency probably always results in sympathetic hypostimulation. The cardinal symptoms of Addison's disease can readily be explained on this basis. Hypostimulation of the cardiac accelerator and vasoconstrictor fibers, both of which are sympathetic, must result in corresponding atony of the entire cardiovascular system. The profound asthenia associated with adrenal insufficiency probably is due in part to vascular hypotension and in part to the relative atony of the skeletal musculature.

Hypotension also plays an important rôle in the phenomena of shock, but the rôle of the vasomotor mechanism in the production of hypotension in shock is not fully known. As early as 1870, Goltz observed vagus arrest of the heart and loss of arterial tonus due to a blow on the exposed mesentery of a suspended frog. Under these conditions, the blood tended to accumulate in the splanchnic area in obedience to the law of gravity. That splanchnic vasodilatation plays a rôle in shock must be conceded. It is now well known, however, that the low blood pressure characteristic of shock cannot be explained on the basis of splanchnic vasodilatation alone. The various factors involved in this condition cannot be discussed in the present volume. In view of the important rôle of the splanchno-peripheral vasomotor balance in the distribution of blood volume and the permeability of the vascular endothelium, it may be assumed that the vasomotor nervous mechanism plays an important rôle in the production of low blood pressure in shock as well as in various other disease processes.

Some Factors Involved in Pulmonary Engorgement and Hemorrhage.—The pulmonary vessels are subject to direct vasomotor control only in a relatively slight degree, if at all. The lungs also receive blood through the bronchial arteries which arise directly from the aorta. In cases of hemoptysis involving only the pulmonary vessels, any measure which constricts the systemic vessels, *e. g.*, the administration of adrenalin, may aggravate the bleeding by forcing blood from the systemic into the pulmonary vessels. On the other hand, measures which bring about vasodilatation, *e. g.*, the administration of nitrites, tend to diminish the engorgement of the lung by diverting blood into the systemic vessels. Hemoptysis due to necrosis of lung tissue may involve both pulmonary and bronchial vessels. The former, being the more numerous, are more likely to be eroded. Yet, even though a bronchial artery were the source of the hemorrhage, the production of vasoconstriction by

means of styptic drugs might still be harmful because a general rise in blood pressure and consequent turgescence of the lungs would tend to bring about hemorrhage at other weak points. On the other hand, measures which produce wide-spread vasodilatation might be beneficial because of their tendency to divert blood from the lungs, which would also counterbalance the risks of reopening the bleeding point. Lowered blood pressure would also favor the sealing of bleeding points by means of blood clots. The relief of asthmatic attacks by the administration of adrenalin probably is due mainly to its constricting effect on the vessels in the bronchial mucosa.

Regulation of Cerebral Blood Pressure and Cerebral Hemorrhage.—Although the cerebral vessels are supplied by vasomotor nerves, these nerves seem to play only a minor rôle in the regulation of the blood supply to the brain. All the cerebral vasomotor effects ordinarily observed can be readily explained without reference to these nerves.

The liquid content of the cranium, consisting of the blood and cerebrospinal fluid is a constant volume, since the cranial wall is rigid and the brain substance is incompressible. If the volume of blood in the cerebral vessels is increased, cerebrospinal fluid must be expressed from the cranium. This is the first effect of a rise of arterial pressure in the brain. The cerebral sinuses then become compressed until the pressure in them equals that exerted against their walls by the brain substance. Since the medulla oblongata contains vital centers, its blood supply must be maintained at all hazards. If the blood supply to the medulla oblongata becomes inadequate, the resulting cerebral ischemia stimulates the vasomotor center to contract the splanchnic vessels. This results in forcing more blood to the brain. Dilatation of the splanchnic vessels, on the other hand, results in the withdrawal of blood from the brain. The blood supply to the brain is controlled mainly by the vascular reactions of the splanchnic region, which in turn is controlled by the vasomotor center in the brain.

As shown by the results of animal experiments carried out by Cushing, the general blood pressure must be kept at a level somewhat higher than that of the intracranial pressure in order to avoid cerebral ischemia. When the intracranial pressure was increased by the introduction of a saline solution into the cranial cavity from a pressure bottle, no effects other than a slight increase in the pulse- and respiration-rates were observed until the intracranial pressure exceeded the blood pressure. Even these effects could be avoided if the fluid did not affect the sensitive dura. When the intracranial pressure exceeded the blood pressure, the splanchnic vessels contracted and the blood pressure was raised until it again exceeded the intracranial pressure. By repeatedly increasing the intracranial pressure the blood pressure was forced to a level above 200 mm. of

mercury before the vasomotor center showed signs of giving way. When the increased intracranial pressure was relieved, the splanchnic vessels dilated, bringing about a corresponding diminution of blood pressure. If the vagi were divided before the intracranial pressure was modified, in these experiments, the blood pressure corresponded even more closely to the intracranial pressure, but always remained slightly higher than the latter. That the adjustment of the blood pressure to the intracranial pressure was brought about by vasoconstriction in the rest of the body was also shown by the fact that no rise in blood pressure took place in response to increasing the intracranial pressure, following section of both the vagi and spinal cord.

These experimental data have a practical bearing on the treatment of cerebral hemorrhage. Measures designed to reduce the blood pressure to a level low enough to check the hemorrhage are fraught with danger because of the reduction of the blood supply to the medulla oblongata. Furthermore, since the blood supply is automatically maintained at a higher level than the intracranial pressure a vicious circle is established; the hemorrhage increases the intracranial pressure, and the increased pressure causes a rise in blood pressure, which tends to increase the hemorrhage. In general, a rising blood pressure in cerebral hemorrhage indicates a grave prognosis because it shows that the bleeding has not ceased. Direct lowering of the intracranial pressure by means of a lumbar puncture tends to reduce blood pressure by reason of its effect on the vasomotor center; consequently, it tends to check the hemorrhage. On the other hand, such lowering of the intracranial pressure is not without danger, in certain cases, since it reduces the support of the cerebral arteries and renders them more liable to bleed. Since the blood pressure falls immediately following reduction of intracranial pressure, however, the necessity for support of the arteries is also diminished.

On the basis of Cushing's experiments, it seems highly probable that, when more than one hemorrhage into the brain substance occurs, the smaller hemorrhages are usually caused by the effect of the larger primary hemorrhage on blood pressure. The primary hemorrhage increases the intracranial pressure, which in turn, by reason of its stimulating effect on the vasomotor center, raises the general blood pressure to a level at which the weakened arteries in other parts of the brain, particularly the pons, are unable to withstand the strain.

REFLEX DISORDERS OF THE DIGESTIVE TRACT.

Spastic Obstruction.—Since the digestive tube receives inhibitory impulses mainly through the sympathetic, and excitatory impulses

mainly through the parasympathetic division of the autonomic system, sympathetic stimulation results in retardation and parasympathetic stimulation in acceleration of gastro-intestinal activity. Any disturbance in the functional balance of the autonomic system is, therefore, reflected in gastro-intestinal activity.

The functional activities of the esophagus seem to be dominated by its parasympathetic innervation. Under certain conditions, this division of the digestive tube reacts to nervous influences in a manner which affects the entire digestive system. In the case of a neoplasm near the cardiac orifice, the lower portion of the esophagus may become more or less permanently contracted and thus obstruct the passage of food into the stomach, although the new growth, by reason of its small size, plays no mechanical rôle in the occlusion of the cardiac orifice. Globus hystericus also involves spasm of the lower portion of the esophagus. The actual point of constriction may pass up and down in the manner of a peristaltic wave. The patient is unable to swallow, yet, no organic disease is present. Constriction of the esophageal musculature is brought about by parasympathetic overstimulation. In the case of globus hystericus, the cause of esophageal spasm is to be sought in a psychic disorder. In most other instances, esophageal spasm must be regarded as a reflex response to afferent stimulation. For example, malignant disease of the stomach may give rise to reflex contraction of the esophageal musculature. In certain cases, esophageal spasm constitutes the earliest objective evidence of organic disease of the stomach (Langdon Brown, 1923).

So-called "cardiospasm," according to Hurst (1911), is not an active spasm of the cardiac sphincter, but a failure of that sphincter to relax. He, therefore, proposed the term *achalazia* as more accurately descriptive of this condition. That there is a real difference between achalazia and an active spasm is indicated by Hurst's observation that a mercury tube in the esophagus can open the cardiac sphincter by its own weight. It is not improbable, however, that the failure of the cardiac sphincter to relax is often due to just the conditions which excite active spasm in other parts of the digestive tube. As Hurst pointed out, it is often associated with organic disease of the stomach or intestine.

Pylorospasm may be brought about reflexly by a wide variety of causes, *e. g.*, gastric ulcer, appendicitis, renal calculus, pyelitis, and sometimes disease of the gall bladder or the genitalia. Occasionally it occurs as a simple neurosis. If the spasm is slight and of short duration it may be relatively unimportant, but if marked and persistent, it results in gastric dilatation. In some cases, dilatation may be delayed for a long time by the initial compensatory hypertrophy of the stomach wall.

Hypertrophies of Infancy.—On the basis of extensive clinical observations, Fraser (1926) advanced the theory that congenital hypertrophy of the pylorus, hypertrophic ileal obstruction, and congenital hypertrophy and dilatation of the colon have their cause in disturbances of the autonomic nervous system. The essential lesion in congenital hypertrophy of the pylorus is a hypertrophy of the muscular coats of the pyloric canal and antrum and, to a slight degree, of the distal portion of the corpus of the stomach. This is essentially the portion of the gastric musculature which is concerned with the expulsion of the stomach contents. Roentgen-ray examination, according to Fraser, shows ill-timed and abnormal, yet forcible and prolonged contractions of the stomach, under these conditions, but the stomach content is not expelled. On the basis of his findings, he supported the theory, first enunciated by Thomson, that "the muscle is hypertrophied because from an early period in its development it has been worried into overgrowth by constantly recurring overaction, such as would result from even a slight degree of habitual incoördination." The underlying causes of this disease are still obscure, but the marked tendency of smooth muscle to undergo hypertrophy as a result of repeated forcible contractions is well known. Furthermore, the demonstrable abnormal activity of the hypertrophied muscle strongly suggests a functional cause. The older theory of congenital redundancy is no longer tenable.

Hypertrophic ileal obstruction in infants usually involves the lower portion of the small intestine. In 3 cases reported by Fraser (1926), the lower segment of the ileum approximately 6 inches in length was markedly hypertrophied, but the ileocolic sphincter was not involved. Above the hypertrophied segment the ileum was markedly dilated. On the basis of the findings in these cases, Fraser advanced the opinion that this disease is similar in origin to congenital hypertrophy of the pylorus.

Congenital hypertrophy and dilatation of the colon resembles congenital hypertrophy of the pylorus and hypertrophic obstruction of the ileum both in pathology and in the fact that it involves a portion of the digestive tube on the proximal side of a sphincter. Usually the lower limit of the change is at the junction of the colon with the rectum (O'Beirne's sphincter). Occasionally, the hypertrophy and dilatation extend downward to the anal sphincter. This similarity and the fact that the disease first becomes evident in the weeks immediately succeeding birth strongly suggest a similar etiology. According to Fraser, the evidence in all these conditions suggests that the chief etiological factor is a neuromuscular error, resulting in "an uncontrolled contractive function, a delay in the acquisition of the power of inhibition, combined, it may be, with achalasia, and insufficient relaxation of the associated sphincters."

Intussusception.—If the above interpretation of the rôle of the autonomic innervation in the gastro-intestinal hypertrophies of early infancy is correct, it may be assumed that the distinctive feature of autonomic nervous dysfunction, during the early weeks and months of life, is localized hypertrophy. The autonomic dysfunctions of a later period are characterized by exaggeration of the normal functions of the gastro-intestinal musculature. Intussusception occurs most commonly during the period extending from the sixth month to the end of the second year. Of 300 cases of intussusception operated upon in the Edinburgh Children's Hospital, according to Fraser (1926), 295 had their beginning in the lower end of the ileum, where the original point of the invagination remained apparent after the reduction. The peristaltic rush consists of an advancing wave of contraction preceded by a wave of relaxation. As long as inhibition precedes contraction, no harm can result, but if, when the wave of contraction reaches the lower end of the ileum, the inhibition phase is not transmitted, by reason of failure of the inhibitory mechanism, the strong contraction of the peristaltic rush may carry a portion of the gut into the distal segment as an invagination, thus initiating the intussusception. According to Fraser, intussusception occurs most commonly in cases in which the ileocecal segment has not become completely fixed to the posterior abdominal wall, and is provided with a loose mesenteric attachment. There is no adequate reason to assume that this condition favors the initiation of intussusception, although it does offer a mechanical explanation of migration of the intussuscepting segment. The evidence strongly suggests failure of the coördinating mechanism controlling the ileocecal segment.

Reflex Dyspepsia.—Regarding reflex dyspepsia, Moore (1915) wrote: "The gastric functions may be disordered reflexly by a lesion situated more or less remote from the stomach itself. The two essential factors in the production of this condition are the existence of such a lesion and an increased susceptibility of the reflex nervous mechanism. These may vary indirectly. Thus, some lesions, *e. g.*, duodenal ulcer, may assert their existence through a nervous mechanism little more susceptible than the normal, while others, as some ileocecal lesions, may remain latent until the susceptibility becomes greatly exaggerated. There is little doubt that many such cases were formerly classed as nervous dyspepsia. The chief lesions are duodenal ulcer, cholecystitis, chronic appendicular lesions, ileal kinks, chronic ileocecal inflammations, cecal and colonic stagnations, diseases of the generative organs in females, mobility of the kidneys, and diseases of the central nervous system." In many cases of gastric disorder, the stomach itself is not at fault, but is made irritable by the reflex effects of a lesion elsewhere.

Whenever gastric symptoms are strikingly intermittent, it is safe to assume, in the absence of unmistakable evidence of a gastric lesion, that the lesion is located outside the stomach. In view of these considerations, it must be clear that if a patient can at times eat freely of any ordinary food without distress, and at other times rejects all food or suffers pain regardless of what he eats, the stomach itself probably is not at fault. Such intermittent attacks are not uncommonly due to lesions of the gall bladder or the appendix. It is still maintained by some that gall stones may remain for years in the gall bladder without producing symptoms. In general, this is not true, unless the statement refers only to symptoms referable to the gall bladder. Patients with gall stones commonly exhibit symptoms of intermittent gastric irritability. A slight alteration in the position of the stone, or a slight increase in the associated cholecystitis may at any time call forth violent reflex irritation of the stomach and spasm of the pylorus.

In general, it may be stated that the nearer the lesion is to the stomach, the more likely are reflex gastric symptoms to occur. Duodenal ulcer almost invariably calls forth marked reflex gastric symptoms. The same is true of gall-bladder disease. Pancreatitis not only gives rise to reflex disturbances set up by the pancreatic lesion, but also results in inadequate neutralization of the gastric juice in consequence of diminished pancreatic secretion. The symptoms associated with this condition, including those of intestinal obstruction, testify to the wide-spread sympathetic inhibition produced (Langdon Brown, 1923). Reflex gastric disturbances resulting from lesions farther removed from the stomach are less common, but not infrequent.

Just as spastic contraction of a sphincter or gastro-intestinal hypermotility may be brought about through the autonomic nerves, so a segment of the digestive tube may be inhibited, resulting in its dilatation. Atonic dilatation of the stomach, brought about by sympathetic overstimulation, may explain many cases of chronic indigestion. According to Hurst (1911), patients with this condition usually complain of feeling full as soon as they start eating because the dilated stomach cannot relax further, as the normal stomach does when food is ingested; consequently, the intragastric pressure rises. Fibrosis of the stomach gives rise to the same symptoms, because also in this condition the stomach is incapable of relaxation. Obstructive dilatation of the stomach differs from atonic dilatation in that it is usually associated with powerful peristaltic waves under which the gastric musculature gives way, but, in many cases, violent peristalsis still occurs after the stomach is enormously distended. Obviously, parasympathetic overstimulation plays an important rôle in these cases.

GASTRIC AND DUODENAL ULCER.

That gastric and duodenal ulcers are commonly associated with parasympathetic hypertonus has long been recognized. As early as 1913 von Bergman expressed the opinion that the entire complex of nervous symptoms associated with gastric and duodenal ulcer is referable to a disharmony of the autonomic nervous system which manifests itself in vasomotor disturbances, resulting in ischemia and spasticity of the gastro-intestinal tract. He regarded this as the real cause of the ulcerative process. Kaufmann (1913) regarded leukopenia as one of the signs of the constitutional disturbance responsible for gastric and duodenal ulcer. He had previously called attention to a deficiency of gastric secretion as one of the contributing factors in the genesis of gastric lesions. More recently he also emphasized the rôle of gastro-intestinal spasticity which he regarded as a result of the underlying constitutional disturbance and not of the ulcerative lesion. He also regarded psychic disturbances and over-exertion of any kind as important factors in the genesis of gastric and duodenal ulcer. These observations regarding the rôle of vasomotor disturbances and leukopenia associated with gastric and duodenal ulcer become increasingly important in view of the evidence advanced by Müller (1926), that disturbances in the functional balance of the autonomic nervous system are accompanied by regional changes in the permeability of the blood vessels and the distribution of leukocytes. According to Mucci (1926), ulcer formation is a direct result of a loss of functional balance between the sympathetic and parasympathetic innervation of the digestive tube, which may be of emotional or toxic origin or both, but develops only with a constitutional tendency to gastro-intestinal neuroses. On the basis of extensive clinical and experimental studies, Müller (1926) advanced the opinion that chronic gastric and duodenal ulcers have their cause in a chronic constitutional disorder, one of the chief manifestations of which is a lack of balance between sympathetic and parasympathetic tonus. According to his view, slight irregularities in the general body economy, *e. g.*, dietary indiscretions, psychic disturbances, exposure, etc., which, under normal functional conditions of the autonomic nervous system, give rise to visceral disturbances which are relatively unimportant and of short duration, may, if the functional balance between the sympathetic and parasympathetic nerves is already disturbed by reason of constitutional disorders, result in long-continued excitation of the hyperirritable components of the autonomic innervation of the organ in question. Consequently, in vagotonic individuals, peripheral stimulation, *e. g.*, sunburn, may result in gastro-intestinal hyperexcitation, the duration of which cannot be foretold. Such peripheral stimulation, according to Müller, may, in certain indi-

viduals, actually give rise to gastric or duodenal ulcer. Likewise, in individuals with chronic gastric or duodenal ulcer, the underlying constitutional disorder may give rise to periodic stimulation in the splanchnic area resulting in symptoms of an acute character. The frequent recurrence of gastric and duodenal ulcer, according to Müller, is also referable to the underlying constitutional disorder.

Balint (1927) emphasized the constant association of hyperacidity with vagotonia in ulcer patients and pointed out that the majority of these patients exhibit alkali retention, indicating an acid condition of the tissues. That hyperacidity is an important factor in the causation of gastric and duodenal ulcer is also indicated by a large volume of experimental data bearing on the production and healing of chronic peptic ulcers in animals. In view of all the data available at present, it may be stated that acute and chronic ulcers belong to the same category pathologically, but are entirely distinct both clinically and therapeutically. In the case of acute ulcer, treatment should be directed to the ulcer itself. Its healing may be regarded as terminating the disease. In the case of chronic ulcer, treatment should be directed to the underlying constitutional disorder, since the ulcer is but a symptom of the disease. This is in full accord with the long-recognized clinical teaching that chronic gastric and duodenal ulcers cannot be cured by resection of the ulcerative lesions. It also emphasizes the importance of chronic gastric and duodenal ulcer as an indication of local or general autonomic dysfunction.

VISCERO-CUTANEOUS AND CUTANEO-VISCERAL REFLEXES.

The Mechanism of Viscero-motor and Viscero-cutaneous Reflexes.—That a visceral lesion may give rise to reflex muscular rigidity, cutaneous ischemia, and hyperesthesia in a peripheral area innervated from the same segments of the spinal cord as the viscus in question has long been known. The muscular rigidity is due to visceromotor reflexes set up by stimulation of the general visceral afferent fibers supplying the diseased viscus and carried out through somatic efferent neurons. Cutaneous ischemia is elicited by the same afferent stimulation, but the efferent impulses are carried out through general visceral efferent and sympathetic (vasomotor) neurons. The sensory cutaneous manifestations associated with visceral lesions were explained by many of the older investigators, particularly Head and Mackenzie, on the basis of viscerosensory reflexes. According to Mackenzie's conception, viscerosensory reflexes are not reflexes in the ordinary sense. He regarded cutaneous hyperesthesia as the result of overstimulation, by visceral afferent impulses, of afferent neurons in the spinal cord which normally convey impulses arising in the cutaneous area in question. Accord-

ing to this theory, the spinal cord cells become hyperirritable by reason of visceral overstimulation; consequently, their threshold of stimulation for peripheral impulses is lowered, so that slight stimulation of the cutaneous receptors results in pain.

Wernoe (1920-1925) has emphasized the rôle of viscerocutaneous reflexes in the production of cutaneous hyperesthesia. In extensive clinical studies, he commonly found cutaneous hyperesthesia associated with localized vasoconstriction in the same area. In general, the area of cutaneous ischemia coincided exactly with the hyperesthetic area. On the basis of these clinical findings and the results of animal experimentation, Wernoe concluded that cutaneous hyperesthesia associated with visceral disease probably does not depend on hyperirritability of spinal cord cells produced by visceral stimulation, but is due to the effect on the peripheral receptors of the changes brought about in the skin through viscerocutaneous reflexes (see Chapter XVII).

Effects of Localized Cutaneous Stimulation on Visceral Organs.—Just as localized visceral stimulation brings about changes at the periphery through viscerocutaneous and visceromotor reflexes, so localized cutaneous stimulation brings about changes in visceral organs through cutaneo-visceral reflexes. The principle of counterirritation, long recognized and applied in medical practice, probably has its basis in cutaneo-visceral reflexes. In a recent study, by means of the fluoroscope, of the effect on gastric tonus and motility of localized thermal stimulation of the skin, Freude and Ruhmann (1926) found that such stimulation in the epigastric region elicited responses in the stomach within a few seconds. Regarding gastric motility, they found that, in general, cold applications first inhibit peristalsis, but after a short interval stimulate irregular short peristaltic waves and at the same time bring about reduction or cessation of activity of the pyloric sphincter. Hot applications stimulate gastric peristalsis and bring about more frequent opening of the pylorus. A hyperirritable stomach is soothed, *i. e.*, preëxisting hyperperistalsis is inhibited, by hot applications. Regarding changes in gastric tonus, they found that a preëxisting normal or subnormal tonus is still further diminished by cold, but increased by hot applications. On the other hand, if the stomach is hypertonic its tonicity is still further increased by cold and inhibited by hot applications. In case of heterotonicity, the condition is aggravated by cold and alleviated by hot applications. In their experiments, gastric spasm was not appreciably influenced by cold, neither was it relieved by hot applications. Neither did cold applications appreciably influence pylorospasm and consequent atonicity of the gastric musculature. This condition was relieved, however, by hot applications. In general, according to their findings, the effect on the stomach of cold applications is similar to

inhibition produced by sympathetic stimulation, and that of hot applications to the effect of parasympathetic stimulation.

More recently, Ruhmann (1927) showed that visceral reactions similar to those elicited by localized thermal stimulation of the skin may also be elicited by localized mechanical and chemical cutaneous stimulation, and that the visceral response comes about only after a change in the tonic condition of the cutaneous blood vessels in the area stimulated has taken place. Furthermore, the visceral organ affected undergoes a vasomotor change corresponding to the localized vasomotor change in the skin, *i. e.*, cutaneous hyperemia results in hyperemia, and cutaneous ischemia results in ischemia of the visceral organs in question. These findings are in full accord with the finding of Boas (1926) that bleeding of a gastric ulcer may be provoked by hot applications in the epigastric region. This fact, as pointed out by Boas, proves that hot applications which produce cutaneous hyperemia also produce hyperemia in the corresponding visceral organs.

The healing effect of visceral hyperemia produced by localized cutaneous stimulation has been quite generally recognized, but the mechanism by which such visceral hyperemia is brought about is still in question. Neither have the clinical possibilities of localized cutaneous stimulation in visceral disease been fully appreciated.

Reflex Character of Visceral Reactions to Localized Cutaneous Stimulation.—Not a few clinical investigators, including Ludin (1919) and Boas (1926), have maintained that the effect on a visceral organ of heat applied to a localized cutaneous area is produced by increased temperature of the viscus due to direct penetration of heat through the tissues. Many of the data available do not support this theory. For example, strong thermal stimulation of the skin in the epigastric region lasting for several hours does not result in a change in temperature of more than one degree in the stomach (Winternitz, 1871; Chelmonski, 1894; Iselin, 1911; Ludin, 1919). The fact that other means of stimulation which result in localized cutaneous hyperemia produce hyperemia in the corresponding visceral organs also speaks against this theory.

That the various reactions of the stomach, including vasomotor changes, obtained by Freude and Ruhmann by localized thermal stimulation of the skin, are reflex reactions is indicated by the fact that the stomach reacts only when the stimulus is applied in the cutaneous zone which receives its innervation from the segments of the spinal cord which also supply the stomach, and that when the stimulus is applied in this zone, the reaction of the stomach follows almost immediately. The fact that the vasomotor change in the viscus corresponds to the vasomotor change produced in the cutaneous area stimulated also indicates that localized cutaneous stimulation results in a like autonomic orientation in the cutaneous

area and the viscera innervated through the same segments of the spinal cord, *i. e.*, localized stimuli which result in cutaneous ischemia produce intrasegmental parasympathetic stimulation. The reflex centers involved are located segmentally in the spinal cord.

In view of the facility with which cutaneous stimulation elicits reflex visceral reactions, particularly vasomotor changes and changes in the tonic state of the visceral musculature, it must be apparent that many visceral disorders, particularly disorders of the gastrointestinal canal, may be influenced beneficially by appropriate stimulation of the corresponding cutaneous area.

CHAPTER XX.

SURGERY OF THE AUTONOMIC NERVOUS SYSTEM.

PERIARTERIAL SYMPATHECTOMY.

Historical Survey.—The operation commonly known as periarterial sympathectomy consists essentially in removing the adventitia, with the nerve plexus contained in it, from a segment of the vessel several centimeters in length. This operation has been employed in a wide variety of clinical conditions involving the blood supply of the extremities. The literature relating to it has, during recent years, grown enormous. A complete review of this literature, in the present connection, would be superfluous.

Jobulay attempted denervation of certain arteries by cutting as many as possible of the nerves which approach them as early as 1899. In 1901 Higier recommended tearing the nerve plexus around the femoral artery in cases of intermittent claudication. Priority in periarterial sympathectomy involving the removal of a segment of the adventitia is commonly accorded to Leriche. Early in 1917, Leriche and Heitz reported 2 cases of severe causalgia of the median nerve, following war wounds, in which pain was relieved by resection of the sheath of the brachial artery. Later in the same year, Leriche reported 37 cases of obstinate fractures and causalgia in which he divided the periarterial nerve plexus. He claimed complete success in 16 of these cases and fairly good results in some of the others in which the surgical treatment was followed by proper massage and muscle training. Since that time, Leriche employed periarterial sympathectomy in a wide variety of clinical conditions. Although it has not given relief in all cases, he claims a high percentage of successes. According to published reports by himself and others (Penfield, 1925; Brüning, 1927), this operation has, in his hands, been followed by success in cases of causalgia, Raynaud's disease, trophic and post-traumatic ulcers, various edemas and skin diseases, and a variety of other clinical conditions.

Periarterial sympathectomy was introduced in Germany by Brüning, who, with Förster (1922), reported lasting beneficial results of the operation in cases of Raynaud's disease and scleroderma. Brüning (1923) also reported beneficial results of periarterial sympathectomy in cases of trophic and vasomotor disturbances and in beginning gangrene. In a recent paper in which he discussed the innervation of the peripheral arteries in relation to periarterial

sympathectomy, Brüning (1927) still maintained that this operation, if properly carried out, invariably results in diminution of the tonus of the arterial musculature and consequent hyperemia.

Not a few other investigators have also reported beneficial results of periarterial sympathectomy in certain cases, but also a high percentage of failures. Kümmell (1924) reported improvement over a considerable period in 3 out of 4 cases of Raynaud's disease, 2 out of 3 cases of freezing gangrene, and 3 out of 8 trophoneurotic lesions. He expressed the opinion that the method should be tried in all groups in which such results had been obtained. Rieder (1924) reported 4 cures out of 23 cases and 1 death due to pulmonary embolism following thrombosis of the femoral artery in connection with the operation. Stahl (1926) reported complete success in 7 (3 scleroderma, 2 Raynaud's gangrene, 1 ulcer after freezing, 1 neuropathic ulcer), complete failure in 5 (2 scleroderma, 1 Raynaud's, 1 trophic ulcer, 1 endarteritis), and death due to pulmonary embolism following thrombosis in the region of the operation in 1 out of 15 cases. Two cases could not be followed. Polak (1926) reported results which seemed promising immediately after the operation, but no lasting benefit in 5 cases of trophoneurotic ulcers of various origins. In 9 gynecological cases in which the dominant symptom was lumbar pain, Bittman (1926) decorticated the abdominal aorta for a stretch of 8 to 12 cm., including 4 cm. of the common iliac arteries, with alleviation of the pain. The constant success in these cases lead him to conclude that the pain was due to visceral neuroses and that it subsided by reason of the interruption of conducting pathways.

Reports of similar character could be multiplied almost indefinitely from the literature available at present. In general, it may be stated that not a few who have carried out periarterial sympathectomy and observed the results in a variety of cases still regard it as a surgical procedure to be recommended particularly in cases in which an increased blood supply to the extremity promises relief, if the artery in question is not organically diseased. Others reject periarterial sympathectomy both on the basis of observed results of the operation and the present status of our knowledge of the innervation of the peripheral arteries.

Anatomical and Physiological Considerations.—The arteries of the extremities derive their nerve supply chiefly through branches of the peripheral nerves in proximity with which they lie. These branches, which include both fibers of sympathetic and spinal ganglion origin, join the peripheral arteries at intervals throughout their entire extent (Chapter VII). Although the periarterial nerve plexuses on the brachial and femoral arteries are continuous with the plexus on the aorta, it cannot be assumed, in the light of the most recent anatomical findings, that offsets from the plexuses on

the aorta contribute materially to the innervation of the more distal portions of the peripheral arteries, nor that any considerable number of long fibers extend distally even in the proximal portions of the periarterial plexuses associated with these arteries. Consequently, periarterial sympathectomy does not bring about sympathetic denervation of a peripheral artery.

In view of the anatomical relationships of the nerves supplying the peripheral arteries, numerous attempts have been made to explain the results reported following periarterial sympathectomy. That the immediate result of this operation is a primary stage of local contraction of the denuded artery which is followed by a secondary stage of vasodilatation associated with increased pressure, as compared with that of the opposite side, and a local increase of several degrees in skin temperature is quite generally conceded. According to Leriche and Heitz (1917), periarterial sympathectomy is followed by all the signs of an active vasodilatation, but after a few weeks the vasomotor reactions return to the preoperative state. They also maintained that resection of an obliterated arterial cord provokes a vasodilatation which is more persistent than that which follows periarterial sympathectomy, but always tends to return to normal. According to Leriche and Fontaine (1927), resection of an obliterated subcutaneous venous cord, in certain cases, also produces an active vasodilatation. They even reported that the vasomotor effects of a single unilateral operation extended to all four limbs in certain cases. Such observations strongly suggest that the results of periarterial sympathectomy are not due to section of efferent fibers alone, but must be due, at least in part, to reflex vasomotor phenomena which, according to Leriche and Robeneau (1927), result in a general vasodilatation, but the effect is most marked in the limb subjected to operation. According to Colle and Pecco (1928), periarterial sympathectomy induces vasodilatation and hyperdistensibility of the vessels in the entire region dependent on the arterial tree which is the site of the intervention and sometimes also in neighboring regions. It also causes a lability of the walls of the arteries affected by it.

In view of the reported favorable results of the operation, there seems to be no reason to doubt that periarterial sympathectomy has resulted in a more or less permanent increase in the blood supply to the extremity and lasting benefit in many cases in which the blood supply of the extremity was restricted before the operation. Neither can it be denied that the operation was a factor in alleviating pain in many instances.

Not a few investigators have supported the theory that all the beneficial results observed, following periarterial sympathectomy, are due to hyperemia resulting from partial sympathetic denervation of the artery (Kappis, 1922, 1923; Kulenkampff, 1923; Drevermann,

1923; Seifert, 1922; and others). Others have supported the theory that periarterial sympathectomy results in a change in the tonic condition of the entire sympathetic system by reason of the reflex effect of stimulation of the sensory fibers supplying the artery (Läwen, 1922; W. Lehmann, 1924; Kümmell, 1923; Kreiblich, 1923; Polak, 1926; and others). Still others advanced the opinion that the hyperemia following periarterial sympathectomy is due to stimulation of short duration caused by section of the small fiber bundles along the artery (Kreuter, 1923; Rieder, 1924; E. P. Lehmann, 1924). On the basis of results obtained in animal experiments, Klug (1924) denied the occurrence of an actual increase in circulation through the extremity following periarterial sympathectomy. On the basis of the results of microscopic studies of the capillaries, Magnus (1926) opposed the theory that the changes observed following periarterial sympathectomy are due to reflex effects of the operation and advanced the opinion that the local increase in temperature is a result of traumatic disturbance of the circulation. Weidhopf (1923, 1924) correlated the hyperemia following operation with a preceding ischemia. Brüning (1927) advanced the theory that interruption of the periarterial nerve plexus, which is made up mainly of nerve components which join the artery through branches of the spinal nerves and maintains a tonus which may be regulated through the vasoconstrictors, results in a lowering of this tonus and consequent hyperemia, but he did not attempt to explain just how this is brought about.

The subsidence of pain following periarterial sympathectomy is no less difficult of explanation, on the basis of our present knowledge of the innervation of the peripheral arteries, than the occurrence of hyperemia. Gundermann (1923), like Leriche, supported the theory that the subsidence of pain is a result of improved circulation and nutrition. Brüning (1923) and Drevermann (1923) regarded it as a result of the absence of angiospasm. W. Lehmann (1924) explained the subsidence of pain on the basis of reflex inhibition of the vasoconstrictors in consequence of the removal of centripetal stimuli from the artery or raising of the threshold of stimulation of the sensory fibers supplying the artery or both.

Certain investigators, particularly Friedrich (1924), Shilf and Stahl (1925), and Abrashanow (1927), have advanced experimental data in support of the theory that some sensory fibers supplying a peripheral artery run longitudinally in the periarterial plexus. According to their observations, irritating substances, *e. g.*, lactic acid or barium chloride, injected into the femoral artery of an experimental animal elicit pain reactions, even though all the fibers which join the artery via the sciatic nerve and its branches are cut. In support of the contention that these pain reactions are due to sensitivity of the artery, Abrashanow pointed out that lactic acid

injected into the femoral vein does not elicit pain reactions and that the pain reactions following injection into the femoral artery are intensified by clamping the femoral vein. He assumed that the partial subsidence of pain following periarterial sympathectomy, in certain clinical cases, is due to the cutting of the sensory fibers which run longitudinally in the periarterial plexus.

Although none of the theories cited above seem adequate, in the light of our present knowledge, to explain either the occurrence of hyperemia or the subsidence of pain following periarterial sympathectomy, the facts that some degree of peripheral vasodilatation is a fairly constant result of this operation and that it has resulted in the alleviations of pain in certain cases still remain and cannot be disregarded. Nevertheless, it must be conceded that there is no rational anatomical or physiological basis for this operation as a clinical procedure. Neither do the results reported in the literature justify its indiscriminate application. That it may be employed with advantage in selected cases cannot be denied.

SYMPATHETIC GANGLIONECTOMY AND RAMISECTION.

Definition and Review.—Sympathetic ganglionectomy consists of the removal of one or more ganglia of the sympathetic trunk in order to insure complete interruption of all peripheral connections. Sympathetic ramisection consists in section of the communicating rami connecting one or more ganglia of the sympathetic trunk with the spinal nerves. Surgery of this type is not new. Alexander performed bilateral extirpation of the superior cervical sympathetic ganglion in a case of epilepsy as early as 1889. In 1892 Jacksh resected the vertebral plexus and divided the sympathetic trunk between the middle and inferior cervical ganglia. In 1896 Jaboulay divided the sympathetic trunk both above and below the middle cervical ganglion. All the above operations were carried out in cases of epilepsy. In 1896 Jaboulay also performed sympathetic ganglionectomy in a case of exophthalmic goiter. In 1897 Jonnesco carried out a similar operation in a case of glaucoma. In 1899 Ball extirpated the superior cervical ganglion in a case of glaucoma with atrophy of the optic nerve.

The results of these early operations were not such as to stimulate interest in surgery of the autonomic system, and nearly all the early operative procedures have been discarded. Stimulated by Franck's (1898) discussion of the incidence of angina pectoris in cases of acute exophthalmic goiter and his suggestion that anginal pain may be due to an overflow from the spinal cord of impulses from the cardiac plexus which reach the cord via the inferior cervical and first thoracic sympathetic ganglia, Jonnesco, in 1916, first performed sympathetic ganglionectomy for the relief of anginal pain. Follow-

ing Jonnesco's lead, not a few surgeons became interested in the surgical treatment of angina pectoris, with the result that sympathetic ganglionectomy has become a recognized clinical procedure in the treatment of angina pectoris in selected cases.

The publication in 1924 by Royle and Hunter of their findings in experimental animals and the clinical results of sympathetic ganglionectomy and ramisection in cases of spastic paraplegia gave a tremendous impetus to the study of the functional relationships of the autonomic nervous system and led to the application of surgery involving the sympathetic system in a wide variety of clinical conditions. One of the most important results of this work, on the clinical side, is the extensive application of sympathetic ganglionectomy and ramisection to diseases of the blood vessels.

Sympathectomy in Spastic Paralysis.—The application of sympathetic ganglionectomy and ramisection in the treatment of spasticity of muscles of the extremities, as advocated by Royle and Hunter, was based on the assumption that the plastic component of the tonus of skeletal muscles is mediated through the sympathetic nervous system and that, in the presence of an impaired voluntary nervous mechanism, this component of muscle tonus may become exaggerated, resulting in spasticity. Consequently, removal of the sympathetic innervation ought to relieve the spasticity and give the impaired voluntary nervous mechanism, if not completely destroyed, a chance, by the aid of passive manipulation and other means of reëducation, to resume control of the muscles. This assumption was based on the results of experimental studies on the relation of muscle tonus to the sympathetic nervous system, which were not fully corroborated by the findings of other investigators (see Chapter XV). Royle did not advocate sympathetic ganglionectomy as a cure for spastic paralysis. According to his own statement, "it merely removes a factor which has been interfering with the normal physical education of the individual, and the essential treatment of spastic paralysis is education of the central nervous system."

The clinical results of sympathetic ramisection in Royle's early cases of spastic paraplegia, as set forth in his reports, were highly encouraging. Certain other surgeons also reported beneficial results in some cases. For example, Carrell (1926), who carried out sympathetic ramisection in 35 cases, stated: "Improvement in function has not been marked, but in 15 cases the gait was improved to the extent of more ease in flexing and bending the knee and walking with less rigidity." In the hands of certain other surgeons, notably Kanavel, Pollock, and Davis (1925), sympathetic ganglionectomy and ramisection, in cases of spasticity due to a variety of causes, resulted in no appreciable benefit to the patients. In spite of numerous reported failures and much adverse criticism, Royle

(1926) still maintained, on the basis of results obtained by himself and others, that "the surgical results of ramisection in the treatment of spastic paralysis exceed those of any other method yet suggested." On the basis of the results obtained by sympathectomy in 40 cases treated in the New York Orthopedic Dispensary and Hospital, Von Lackum (1929) concluded that this operation "offers the most effective means of relief in many cases of spastic paralysis in children." According to his report, nearly every patient showed decreased spasticity in the affected extremity while at rest, and approximately two-thirds of the patients showed a striking reduction in rigidity, following sympathectomy, both while active and at rest. The clinical results obtained in the lower extremities were described as excellent in approximately 20 per cent, and as good in over 40 per cent of the cases. Certain patients, particularly children with marked mental deficiency, were not materially benefited by the operation. The results obtained in the upper extremities in a limited number of cases were less favorable than those obtained in the lower extremities. This probably was due in a large measure to less complete sympathetic denervation of the upper extremities. Certain clinical data advanced by Kuré and his associates (1927) also seem to indicate that sympathectomy produces beneficial results in certain cases of spastic paralysis, particularly those in which the spasticity has resulted from a pyramidal lesion. They advanced evidence in support of the view that these cases commonly exhibit exaggerated sympathetic tonus, whereas, cases in which the spasticity is due to an extrapyramidal lesion do not. Consequently, sympathectomy results in diminution of the hypertonus in cases of the former, but not in cases of the latter type.

In general, it may be stated that the results of sympathetic ganglionectomy and ramisection in the treatment of spastic paraplegia and other forms of spastic paralysis, as reported in the majority of cases, have not been such as to warrant the general application of this method of treatment. That it has produced beneficial results in some cases cannot be denied. The anatomical and physiological principles involved in the application of sympathectomy in the treatment of spastic paraplegia need not be discussed more fully in this connection. The functional significance of the sympathetic innervation of skeletal muscles is discussed at length in Chapter XV.

Sympathectomy in Diseases of the Blood Vessels.—The application of sympathetic ganglionectomy and ramisection in the treatment of diseases of the blood vessels is based on a knowledge of the sources and distribution of the sympathetic fibers supplying the vessels of the extremities and the effects of the functional removal of these fibers. In view of the anatomical arrangement of the nerves supplying the peripheral blood vessels (see Chapter VII), it is clear that extirpation of the second, third, and fourth lumbar

sympathetic ganglia or section of the communicating rami joining the nerves of the lumbo-sacral plexus must result in complete sympathetic denervation of the vessels of the lower extremity. Likewise, extirpation of the inferior cervical and first thoracic ganglia or section of the communicating rami joining the brachial plexus must result in complete sympathetic denervation of the vessels of the upper extremity, except in cases in which sympathetic fibers join the brachial plexus from the second thoracic sympathetic ganglion via the inconstant intrathoracic ramus running from the second to the first thoracic nerve. Whenever this ramus joins the first thoracic nerve proximal to the origin of the first intercostal ramus, it constitutes a pathway through which sympathetic fibers derived from the second thoracic ganglion may join the brachial plexus (Kuntz, 1927). This ramus is present in a large percentage of cases. In these cases, complete sympathetic denervation of the upper extremity requires section of the ramus running from the second to the first thoracic nerve or extirpation of the second thoracic ganglion, in addition to extirpation of the inferior cervical and first thoracic ganglia, interruption of the preganglionic fibers which enter these ganglia, or section of the gray communicating rami to the brachial plexus.

This knowledge was applied recently by Adson and Brown (1928) in the surgical treatment of Raynaud's disease. They had previously attempted to relieve this condition in the upper extremity by extirpation of the inferior cervical sympathetic ganglion and cervical ramisection, but without success. In a recent case of Raynaud's disease in the upper extremities, Adson exposed the upper portion of the thoracic sympathetic trunk by a dorsal incision and resection of a segment of the dorsal portion of the second rib, divided the sympathetic trunk below the second thoracic ganglion, and removed a segment of the trunk, including the first and second thoracic ganglia. This operation was first carried out on the right side with complete relief of the symptoms of Raynaud's disease in the right upper extremity. It was carried out later on the left side with the same result in the left upper extremity. In another case in which bilateral extirpation of the inferior cervical ganglion had failed to relieve the symptoms of Raynaud's disease in the upper extremities, bilateral extirpation of a segment of the sympathetic trunk, including the first and second thoracic ganglia, was attended by complete success. That the operation, as carried out in these cases, resulted in complete sympathetic denervation of the upper extremity is evidenced not only by the complete relief of the symptoms of Raynaud's disease, but also by the absence of perspiration and failure to elicit perspiration in the upper extremities by the administration of sudorific drugs. It is also noteworthy that regulation of the cardiac rhythm was not markedly disturbed by

the bilateral operation in these patients, although a portion of the cardiac accelerator fibers must have been interrupted. The physiological results obtained in these cases stand in marked contrast to the results of cervical ramisection in a case of Raynaud's disease reported recently by Fulton (1928). In Fulton's case, cervical and lumbar sympathetic ramisection carried out on the right side resulted in relief of the symptoms of Raynaud's disease in the lower, but not in the upper extremity. The right hand, according to Fulton's report, was not obviously benefited by the operation.

Complete sympathetic denervation of an extremity results in paralysis of the vasoconstrictor nerves supplying its vessels. Consequently, the vessels dilate and the blood supply to the extremity is increased. In normal experimental animals subjected to sympathetic denervation of an extremity, this extremity shows evidence of an increased blood supply only temporarily. According to most observers, circulation returns to approximately the preoperative level, under these conditions, in ten days to two weeks (see Chapter VII). If the vessels of an extremity are constricted by reason of exaggerated vasomotor tonus before operation, sympathetic denervation permits the vessels to dilate and the blood supply to the extremity probably remains permanently increased. There is no reason to assume that the vessels contract beyond their normal size in the readjustment following removal of the vasoconstrictor influence.

In experimental animals, the temporary increase in the circulation in a limb following deprivation of its sympathetic innervation results in a rise in surface temperature and increased redness in any cutaneous area in which this color is not obscured by pigment. A rise in surface temperature and increased redness of the skin of the parts affected is also a constant result of sympathetic ganglionectomy in man. In a careful calorimetric study of the extremities, following lumbar sympathetic ganglionectomy, in 4 cases of spastic paraplegia and 1 case of cerebral palsy, Brown and Adson (1925) found a marked increase in the production and radiation of heat in the legs and feet. Heat production and conduction in the feet were increased by 200 to 900 per cent. The temperature of the skin of the feet was increased 2° to 6° C. Before operation, determinations of skin temperature of the legs and feet showed a decrease toward the periphery. After operation, this condition was reversed; the feet became relatively warmer. The skin also was dry and perspiration was absent. Similar changes in the skin temperature and heat elimination have been found consistently, following sympathectomy, by these investigators, in all cases in which the blood supply to the extremities was diminished before operation. The following tables summarizing the results of careful quantitative studies of skin temperature and heat elimination in the extremities

before and after sympathectomy in cases of Raynaud's disease, spastic paraplegia, and thrombo-angiitis obliterans were supplied by Dr. G. E. Brown.

RAYNAUD'S DISEASE. SUMMARY OF THE CHANGES IN SURFACE TEMPERATURES AND IN THE RATE OF HEAT ELIMINATION IN THE FEET FOLLOWING LUMBAR GANGLIONECTOMY.

Case.	Maximal increase in skin temperatures, °C.			Heat elimination in small calories each minute for each square inch of surface area.	
	Before operation.	After operation.	Increase.	Before.	After.
1	31.2	35.5	4.3	0.51	0.85
2	22.1	36.6	14.5	0.44	1.32
3	23.9	36.1	12.2	0.94	1.04
4	22.2	33.2	11.0	1.21	0.69
5	19.9	32.7	12.8	0.23	1.17
6	15.0	33.2	18.2	0.39	1.03
Average values			12.1	0.62	1.01

SPASTIC PARAPLEGIA. CHANGES IN SURFACE TEMPERATURE¹ AND IN THE RATE OF HEAT ELIMINATION AFTER LUMBAR GANGLIONECTOMY.

Case.	Maximal increase in skin temperature, °C.		Heat elimination in small calories each minute for each square inch of surface area.	
	Foot.	Lower leg.	Before operation.	After operation.
1	Not recorded	1.5	1.50	3.30
2	2.5	2.0		
3	6.2	3.3	0.30	1.10
4	14.1	Not recorded	0.35	3.90
5	1.1	0.4	1.20	3.00
6	1.6	1.8	0.70	4.10
7	13.8	0.8	0.30	1.40
8	2.0	0.9	0.90	3.50
9	2.4	0.4		
10	4.3	2.7		
11	7.6	0.8	2.25	3.49
12	4.3	7.9		
Average increase	5.2	2.0	0.94	2.90

¹ Final recordings made fifteen to twenty-one days after operation.

The data set forth in these tables show clearly that the blood supply to the extremities, as indicated by heat production and elimination, was markedly increased following sympathectomy in nearly all cases. Obviously, the blood vessels dilate following deprivation of the vasoconstrictor fibers. As in experimental animals, so in man, the blood vessels regain a degree of tonus, following sympathectomy, which probably approaches normal vasomotor tonus, but, if vasomotor tonus was exaggerated before operation, the vessels do not return to the preoperative condition, at

least not for a relatively long time. The results of Brown's studies cited above strongly suggest that, in cases of exaggerated vasomotor tonus, sympathectomy results in a permanent increase in the blood supply to the parts affected, unless the vessels actually become occluded. In view of these considerations and the gratifying clinical results reported in a limited number of cases, the value of sympathetic ganglionectomy and ramisection in the treatment of a variety of vascular diseases characterized by exaggerated vasomotor tonus and spasm, particularly Raynaud's disease and allied conditions, can no longer be questioned.

THROMBO-ANGIITIS OBLITERANS. CHANGES IN SURFACE TEMPERATURE AND RATE OF HEAT ELIMINATION IN THE MOST DISEASED EXTREMITY FOLLOWING LUMBAR GANGLIONECTOMY.

Case.	Increase in surface temperature in toes.		Heat elimination in small calories each minute for each square inch of surface area.	
	Minimal.	Maximal.	Before operation.	After operation.
21	4.2	5.0	1.10	5.00
22	0.6	6.0	0.70	1.50
23	0.8	7.6	0.40	0.70
24	1.3	5.3	0.45	0.70
25	2.7	5.6	0.90	1.60
26	2.3	2.3	0.70	0.60
27	4.7	8.0	0.38	0.98
28	1.9	7.6	0.99	0.62
29	9.8	10.7	0.58	0.61
30	0	3.3	0.83	0.69
31	No postoperative studies carried out; double amputation done.			
32	0	0	0.98	1.50
33	0.4	2.4	0.94	1.04
34	2.9	11.9	0.65	1.90
35	..	8.4		
Average values	2.4	6.0	0.74	1.34

CHANGES IN SURFACE TEMPERATURE AND RATE OF HEAT ELIMINATION ON THE HANDS FOLLOWING BILATERAL THORACIC GANGLIONECTOMY.

Case.	Skin temperature in °C., average of several readings.			Heat elimination in small calories each minute.		Diagnosis.
	Before.	After.	Increase.	Before.	After.	
16	21.0	32.7	11.7	10	34	Raynaud's disease
19	23.3	32.8	9.5	22	80	Raynaud's disease
13	23.6	31.2	7.6	82	118	Arthritis of hands
36	24.9	28.0	3.1	70	140	Scleroderma.

The immediate results of sympathetic ganglionectomy and ramisection in cases of thrombo-angiitis obliterans have been most striking. Yet, it is hardly conceivable that such intervention should arrest the obliterative process. If it alleviates the extreme pain, so common in this disease, and postpones amputation or permits it to be done at a lower level, by reason of the vasodilatation following removal of the vasoconstrictor influences it may be

justified, at least in selected cases. Conservative measures to avoid amputation are the more necessary in these cases because the disease is bilateral, and double amputation is apt to result in economic disaster for the patient who is usually a young or middle-aged man. Brown (1926) emphasized the importance of selecting suitable cases for operation and pointed out the value of the protein reaction as a preoperative test to determine the available capacity for vasodilatation. He found a fairly close parallelism of the rise in skin temperature during protein fever before operation and that following sympathetic ganglionectomy. It would, of course, be futile, as Brown pointed out, to subject the patient to sympathetic ganglionectomy in the absence of any capacity for vasodilatation. Patients with endarteritis obliterans, according to Brown, show only slight capacity for vasodilatation, or none at all. Furthermore, the age and general condition of these patients contra-indicates so drastic an operative procedure.

Sympathectomy in Other Diseases in Which Inadequate Peripheral Circulation is a Factor.—Sympathetic ganglionectomy has also yielded gratifying results in a variety of other pathological conditions which could be benefited by an increased blood supply to the affected parts. The results of this operation in a case of polyarthritis, reported by Rowntree and Brown (1927), are very striking. The patient, a woman, aged thirty-four years, had failed to respond to medical treatment for six years. Her limbs were badly crippled, hands and feet were cold and moist, with trophic changes in the skin and nails, the interphalangeal joints were all enlarged, and the ankles, wrists, elbows, and shoulders showed considerable limitation of motion. Pain was marked over the metatarsal arch and in the wrists, elbows, and knees. Following bilateral extirpation of the second, third, and fourth lumbar sympathetic ganglia, the feet became warm, dry, and pink, the skin desquamated and the trophic changes receded. The pain disappeared entirely in the lower extremities, and the patient was able to walk a distance of $1\frac{1}{2}$ to 2 miles before leaving the hospital. All this is in striking contrast to the condition of the upper extremities which remained cold, clammy, and painful. The surface temperature of the hands was found to be 9° C. lower than the surface temperature of the feet following operation. A later operation involving bilateral extirpation of the inferior cervical and first and second thoracic sympathetic ganglia produced results in the upper extremities similar to those produced by lumbar sympathectomy in the lower extremities (Rowntree, 1929.)

The tendency of trophic ulcers and other trophic lesions of the skin to heal following sympathetic ganglionectomy and ramisection has been observed repeatedly. The beneficial effect of sympathectomy on the healing of wounds has also been demonstrated in

experimental animals. On the basis of a review of the literature and the results of his own experimental studies, Rieder (1927) concluded that infected wounds are not materially influenced by periarterial sympathectomy, but sympathetic ganglionectomy and ramisection always exerts a beneficial effect on both infected and uninfected wounds. In general, the beneficial effect is commensurate with the degree of hyperemia produced.

Sympathectomy in Angina Pectoris.—Sympathectomy in the treatment of angina pectoris was first carried out by Jonnesco in 1916. He assumed that the pain associated with this disease is the result of afferent impulses conveyed from the heart through the visceral afferent components of the sympathetic cardiac nerves. Consequently, he removed the middle and inferior cervical and first thoracic ganglia in order to interrupt the afferent conduction pathways from the heart to the spinal cord. Resection of these ganglia on the left side only sufficed in his first case to relieve the symptoms of angina pectoris in a most striking manner; consequently, the operation was not carried out on the opposite side. In his later operations, Jonnesco removed the superior cervical as well as the middle and inferior cervical and first thoracic sympathetic ganglia. Although the results in Jonnesco's early cases were most satisfactory, they did not stimulate a wide-spread interest in the surgical treatment of angina pectoris because his operation was regarded as too drastic.

In 1923 Coffey and Brown reported 5 cases in which extirpation of the left superior cervical sympathetic ganglion alone, or even section of the superior cardiac nerve and the sympathetic trunk below the superior cervical ganglion sufficed to ameliorate the painful seizures and relieve the main condition of anginal attacks. The results obtained in these cases demonstrated the feasibility of surgical intervention in angina pectoris without extensive operation and without severing the afferent conduction pathways from the heart. They also stimulated interest in the surgical treatment of angina pectoris along these new and simpler lines. Consequently, there is at present an extensive and growing literature bearing on sympathectomy in the treatment of this disease.

Coffey's operation, as carried out in the majority of his later cases, involves section of the sympathetic trunk below the superior cervical ganglion, section of the superior cardiac nerve, and complete extirpation of the superior cervical ganglion on the left side. In cases in which the pain radiates to the right instead of the left side, he advises operation on the right side. His operative procedure is based on the assumption that the anginal attacks are manifestations of spasm of the aorta or coronary arteries or both, and that this spasm is caused by hyperstimulation of the sympathetic fibers supplying these vessels, the majority of which usually arise in the left superior cervical sympathetic ganglion.

Proceeding on the assumption that the impulses which result in anginal pain are conducted by the so-called depressor nerve of the vagus, Hofer cut this nerve on the left side only in some cases and on both sides in others. This procedure apparently relieved the anginal attacks in some cases. This result cannot be attributed to section of afferent vagus fibers, since afferent impulses conducted by vagus fibers probably do not give rise to sensations. Nor could the interruption of afferent vagus fibers obviate the referred anginal pain, since the referred manifestations of angina pectoris involve conduction via the sympathetic trunk and upper thoracic nerves. Furthermore, the so-called depressor nerve probably is not composed of vagus, but of sympathetic fibers in man (Coffey, Brown, and Humber, 1927). According to this view, any amelioration of anginal attacks brought about by section of the so-called depressor nerve must be explained on the same basis as that brought about by section of the superior sympathetic cardiac nerve or extirpation of the superior cervical sympathetic ganglion.

In view of the current teaching that the cardiac accelerator fibers emanate mainly from the middle and inferior cervical and first thoracic ganglia, it has seemed unwise to some to remove these ganglia, by reason of the effect which elimination of the cardiac accelerators might have on cardiac activity. On this basis, Danielopolu, Leriche, and others advised section of the afferent conduction pathways, in the operative treatment of angina pectoris, leaving the cardiac accelerators intact. They proposed extirpation of the superior cervical ganglion and section of all connections of the middle and inferior cervical and first thoracic ganglia with the dorsal nerve roots. This operation would obviate anginal pain by interrupting the sensory fibers, and also remove the chief source of vasoconstrictor fibers to the coronary arteries and proximal portion of the aorta, but leave the motor control of the heart intact. It presents greater technical difficulties, however, than extirpation of the entire cervical sympathetic chain plus the first thoracic ganglion.

A review of the reported cases shows clearly that anginal attacks are ameliorated, at least in some cases, by any of the operative procedures outlined above. On the other hand, none of the operations proposed has brought relief in all cases. In a comparative study of 50 reported cases in which the operative procedures employed were clearly defined and the patients were kept under observation for at least six months following operation, Cutler (1927) found that extirpation of the superior cervical sympathetic ganglion alone, in 16 cases, resulted in definite improvement in 43.7 per cent and at least some benefit in an additional 12.5 per cent of the cases. Extirpation of the entire cervical sympathetic chain plus the first thoracic ganglion, in 25 cases, resulted in definite improvement in 64 per cent and at least some benefit in an additional

8 per cent of the cases. Complete cervical sympathectomy, leaving the first thoracic ganglion intact, in 7 cases, resulted in definite improvement in 57.1 per cent and some benefit in an additional 28.5 per cent of the cases. Section of the sensory fibers without interruption of any motor fibers is practically impossible. This would involve interruption of the fibers connecting the middle and inferior cervical and first thoracic ganglia and the spinal cord either in the main trunk or via the gray rami to the spinal nerves. There are no complete cases of this kind available. The 2 cases reported by Pieri and Leriche are complicated somewhat by interference with the motor fibers. The results were satisfactory in both these cases, but the number is too small to be significant in comparison with the other groups.

In a recent study of 127 surgical cases reported in the literature, together with 8 cases of his own, Hesse (1927) summed up the status as follows: (1) Sympathectomy gives good results in 65 per cent of cases, indifferent results in 17 per cent, and a mortality of 13 per cent. Approximately one-half of the fatal cases are to be attributed to heart failure. Complete cervical sympathectomy resulted in the greatest mortality. Progression of the disease resulted in death later in 10 patients. Partial sympathectomy resulted in 62.6 per cent of cures and 9 per cent of complete failures, as compared with 56 per cent of cures and 18 per cent of complete failures obtained with complete sympathectomy. In his opinion, extirpation of the superior cervical sympathetic ganglion under local anesthesia produces the best results. It was attended by success in 80 per cent of cases and resulted in mortality in only 10 per cent. According to his experience, extirpation of the first thoracic ganglion is poorly borne by a degenerated heart.

In view of the results obtained by the various operative measures employed, it is clear that the amelioration or relief of pain in angina pectoris does not depend on interruption of afferent conduction pathways alone. The satisfactory results reported, in a relatively large number of cases, following extirpation of the left superior cervical sympathetic ganglion alone strongly support the theory that angina pectoris is essentially a disease of the coronary arteries or aorta or both, and that anginal pain results from spastic contraction of these vessels or the resulting ischemia of the cardiac muscle. It is significant to note in this connection that the referred pains of angina pectoris are localized in the same segments in which, according to Head's studies, pains referred from the first part of the aorta are localized. Since the coronary plexuses and the plexus on the first part of the aorta have a common origin, pain referred from the coronary arteries could not be distinguished from that referred from the aorta. Pain referred from the myocardium and the heart valves is usually localized lower in the thorax. This

strongly suggests that, whatever the pathology of angina pectoris, the impulses which give rise to the pain originate in the aorta or coronary arteries. That impulses arising in blood vessels may give rise to pain is well known. Singer (1926) produced pain reactions by stimulating the adventitia of the coronary arteries and aorta, although he could not elicit pain reactions by stimulation of the cardiac muscle or endocardium.

Although a definite pathology of the coronary arteries which is constantly associated with angina pectoris has not been demonstrated, this does not preclude the possibility that the impulses which give rise to anginal pain arise in these arteries. If the pain is due to coronary spasm, the afferent impulses involved may emanate from the coronary arteries, although the cause of the pain is located elsewhere, *e. g.*, in the superior cervical ganglion, the central nervous system, or the heart itself. Danielopolu (1916) advanced the hypothesis that the symptoms of angina pectoris are manifestations of fatigue of the cardiac musculature, due to intoxication of both the sensory and motor elements by fatigue products. This condition is brought about by a temporary deficiency in the blood supply to the myocardium and is maintained by a series of visceral reflexes which he called "pressor reflexes." This theory is still advocated by Danielopolu (1928) in his most recent contribution to the pathogenesis of angina pectoris. Penfield (1925) advanced the theory of "reflex pain." He assumed that axon reflexes from the heart cause vasoconstriction throughout the peripheral area supplied by efferent fibers from one or more sympathetic ganglia, and that the peripheral vasoconstriction stimulates the peripheral end organs for pain.

Although there is no known specific pathology of the heart, coronary arteries, or aorta which is constantly associated with angina pectoris, it seems highly probable that some cardiac pathology exists in every case. Th. and D. Ionescu (1926) based their theory of the origin of the anginal attacks on this assumption. According to their conception, the attack is initiated by direct or reflex stimulation of the heart and vessels, which results in increased work on the part of the cardiac musculature. The disturbance of the coronary circulation further aggravates the unfavorable conditions. They regarded anginal pain as an expression of the unfavorable cardiac condition.

In the majority of the attempts to account for the anginal attacks, spasm of the coronary arteries and the consequent ischemia of the cardiac musculature have played a prominent rôle. Coffey and Brown (1927) regarded coronary spasm as the chief condition of anginal attacks. That such spasm may be brought about reflexly seems highly probable. Anginal attacks are not infrequently precipitated by physical exertion (which in many cases is very slight),

stimulation of the skin by cold, psychic disturbances, etc. In many cases, no exciting cause is apparent. In such cases, impulses arising in the heart or vessels probably elicit reflex coronary spasm. Certain investigators have attempted to explain coronary spasm on the basis of irritative lesions in one or more cervical sympathetic ganglia. While not a few isolated observations indicate that the cervical sympathetic ganglia not infrequently exhibit pathological changes in cases of angina pectoris, these changes cannot be regarded as specific, and there is at present no adequate basis for the assumption that they play an important rôle in the causation of the disease (Clark, 1927).

If it may be assumed that spasm of the aorta or coronary arteries is a primary condition of anginal attacks, as the majority of the data available at present seem to indicate, extirpation of the superior cervical sympathetic ganglion probably is the most rational and most conservative operation yet proposed for the surgical treatment of angina pectoris. According to the results reported by Coffey and Brown, extirpation of the left superior cervical ganglion is sufficient, in the majority of cases suitable for operation, to obviate the anginal attacks. In certain cases, particularly those in which the pain radiates to the right side, extirpation of the right superior cervical ganglion is more effective. Obviously, the beneficial effect of this operation must depend on section of the vasoconstrictor fibers supplying the coronary arteries and proximal portion of the aorta. Elimination of the entire vasoconstrictor supply to these vessels would require extirpation of both superior cervical ganglia. By reason of the anatomical distribution of the right and left superior sympathetic cardiac nerves, however, extirpation of the left superior cervical ganglion eliminates the majority of these fibers in most cases (see Chapter VII).

Extirpation of the superior cervical sympathetic ganglion has not resulted in the relief or amelioration of the anginal attacks in all cases, but neither have the more extensive operations which involve extirpation of the middle and inferior cervical and first thoracic ganglia. Neither is it apparent, on the basis of the reported cases that the more extensive operations produce better results. On the other hand, it has seemed inadvisable to some to remove the inferior cervical and first thoracic ganglia because this procedure not only eliminates a large percentage of the cardiac accelerator fibers, but also interrupts afferent conduction pathways from the heart.

On the basis of a recent experimental and clinical study, Ionescu (1928) advanced the opinion that unilateral extirpation of the inferior cervical and first thoracic ganglia neither impairs the nervous regulation of cardiac rhythm nor eliminates the afferent conduction of impulses from the heart. Furthermore, he maintained, on the basis of functional tests, that the functional capacity

of the heart is not diminished by this operation. In certain cases examined years after the operation, he found no evidence of functional impairment of the heart. He regards the continuance of apparently normal accelerator function and afferent conduction from the heart following this operation as due to the existence of thoracic cardiac nerves (see Chapter VI). These nerves, as shown by Ionescu and Enachescu (1928), like the middle and inferior cervical cardiac nerves, contain both accelerator and visceral afferent fibers. On the basis of these findings, Ionescu regards the objections raised to extirpation of the inferior cervical and first thoracic ganglia, in the treatment of angina pectoris, as without foundation. Nevertheless, extirpation of the middle and inferior cervical and first thoracic ganglia, with or without extirpation of the superior cervical ganglion, must be regarded as a more drastic operation than extirpation of the superior cervical ganglion alone. It also results in more extensive interference with vasomotor control and other visceral functions.

On the basis of clinical observations, Coffey and Brown suggested the possibility of afferent conduction through the superior sympathetic cardiac nerve, and emphasized the necessity, in certain cases, of complete extirpation of the superior cervical ganglion, including its upper pole. Ionescu also recognized this possibility, and pointed out that in those cases of angina pectoris in which the pain radiates into the area of distribution of the cranial and upper cervical nerves, section of the superior cardiac nerve or extirpation of the superior cervical ganglion is necessary, even though the preganglionic fibers to the superior cervical ganglion were severed in removing the lower cervical ganglia.

Obviously, surgical intervention in the treatment of angina pectoris should be considered only in cases which fail to respond to medical treatment. Furthermore, not all these cases are suitable for operation. If the heart has suffered material organic damage and the coronary arteries have become sclerotic, so that they no longer possess the capacity for dilatation, operative intervention may be contra-indicated. In general, it may be stated that, in the presence of organic cardiac disease, the decision must be based on the frequency and severity of the anginal attacks, the functional condition of the heart and blood vessels, and the age and general condition of the patient.

Sympathectomy in Bronchial Asthma.—A survey of the literature bearing on the surgical treatment of bronchial asthma shows that cervical sympathectomy has been applied in the treatment of this disease in many cases, with widely divergent results. In the majority of the reported cases, the entire cervical sympathetic chain was resected unilaterally; in some cases bilaterally. In the hands of certain surgeons, according to their published reports, both

the unilateral and the bilateral operations were successful in a large percentage of cases. Others reported only failures. Kümmell (1924), one of the most ardent advocates of cervical sympathectomy in the treatment of bronchial asthma, reported 17 cases, in 13 of which the superior, middle, and inferior cervical ganglia with the intervening portions of the sympathetic trunk were removed unilaterally, and in the remaining 4, bilaterally. In all but 1 case, according to his report, the asthmatic attacks ceased immediately following the operation. In 4 cases the attacks recurred after two, three, six, and sixteen weeks respectively. On the basis of achieved results, Witzel (1925) also advocated this operation, particularly in obstinate cases of bronchial asthma. Other reports selected at random from the literature are less encouraging. For example, Ramirex and Pool (1925) reported complete failure in 2 severe cases of bronchial asthma in which the entire cervical sympathetic chain was resected on the right side only. In their opinion, these cases demonstrated the futility of unilateral cervical sympathectomy in the treatment of bronchial asthma. Böttner (1925) reported 3 cases in all of which asthmatic attacks recurred following unilateral extirpation of the entire cervical sympathetic chain. Hesse (1927) reported satisfactory results in less than 30 per cent of 17 cases, 12 of which were operated upon unilaterally and 5 bilaterally. He regarded the operation as a failure in the majority of his cases. On the basis of these results and a review of the literature, he concluded that it is too early to form a definite judgment regarding the value of cervical sympathectomy in the treatment of bronchial asthma, but expressed the opinion that the decision probably will be unfavorable.

Both favorable and unfavorable reports of cervical sympathectomy in cases of bronchial asthma could be multiplied from the literature without shedding much additional light on the problem. At present the unfavorable probably outnumber the favorable reports. Yet, in view of the successful operations reported, it cannot be denied that resection of the cervical sympathetic chain on one or both sides resulted in the cessation of asthmatic attacks at least for many months in certain severe cases of bronchial asthma.

The chief aim, in the treatment of bronchial asthma, must always be the relief or prevention of bronchial spasm. According to the current teaching, the bronchoconstrictor fibers are components of the vagus, and the bronchodilator fibers are components of the sympathetic nerves. On the basis of this teaching, the application of cervical sympathectomy in the treatment of bronchial asthma is irrational. In general, vagus stimulation results in bronchoconstriction, and sympathetic stimulation in bronchodilatation. As Dixon and Ransom (1912) have shown in the cat, however, powerful vagus stimulation sometimes results in bronchodilatation. Con-

versely, powerful sympathetic stimulation sometimes results in bronchoconstriction. These results probably are due to the occurrence of some sympathetic fibers in the vagus and some vagus fibers in the cervical sympathetic. Kümmell (1925) maintained, on the basis of careful anatomical studies, that vagus and sympathetic fibers intermingle to such an extent in man that cervical sympathectomy is impossible without cutting fibers of vagus origin. Nor did he admit the correctness of the theory that the bronchoconstrictor fibers are mainly parasympathetic and the bronchodilator fibers mainly sympathetic in man. He also advanced certain data in support of the theory that pathological changes in the cervical sympathetic ganglia play a rôle in the etiology of bronchial asthma. Histological examination of the ganglia removed at operation, in his cases, revealed degenerative changes in the ganglion cells, proliferation of the endothelium of the cell capsules, and, in some cases, sclerotic changes in the small arteries in the ganglia, with inflammatory infiltration. These changes, he believed, resulted in hyperexcitation of the bronchoconstrictor fibers. He also advanced the opinion that the severest cases of the disease also exhibit the most marked pathological changes in the cervical sympathetic ganglia.

There is no reason to question the accuracy of the observations reported by Kümmell. They do not, however, prove the existence of bronchoconstrictor fibers of sympathetic origin. Nor do they demonstrate that pathological changes in the cervical sympathetic ganglia play a rôle in the causation of bronchial asthma. These changes may be accompaniments of the disease, or they may be due to other causes. If the existence of bronchoconstrictor fibers of sympathetic origin were demonstrated, a causal relationship between bronchial asthma and pathological changes in the cervical sympathetic ganglia would be strongly suggested.

According to Braeucker and Kümmell, Jr. (1925), bronchial spasms simulating asthmatic attacks in man, can be brought about in experimental animals (rabbit, ape) by stimulation of the medulla oblongata, vagus, or sympathetic nerves, and other experimental procedures. These spasms do not occur if the bronchial rami of the vagi are divided. Obviously, bronchial spasm may be elicited reflexly. The fact that sympathetic stimulation does not produce bronchial spasm following section of the vagus branches strongly suggests that bronchial spasm produced by sympathetic stimulation may involve reflex excitation of the vagus center in response to stimulation of the general visceral afferent components of the sympathetic nerves supplying the bronchi. In view of these findings and our present knowledge of the innervation of the bronchial musculature and the distribution of visceral afferent fibers to the bronchial mucosa, it seems not improbable that, in those cases of

bronchial asthma in which the asthmatic attacks ceased following cervical sympathectomy, this result may have been due to the interruption of the afferent conduction pathways for impulses arising in the bronchial mucosa, thus preventing reflex spasm of the bronchial musculature. The bilateral effect of unilateral cervical sympathectomy could be explained on the assumption that the distribution of the visceral afferent, like that of the sympathetic fibers supplying the bronchi, is not strictly unilateral, but some fibers cross over to the bronchi of the opposite side.

Sympathectomy in Congenital Megalocolon (Hirschsprung's Disease).—That lumbar sympathectomy or ramisection exerts an influence on the motility of the large intestine has been observed in not a few cases. Such an influence was noted by Royle in the first patient upon whom he performed sympathetic ramisection. More recently, he (1927) reported that "in a series of 25 cases of congenital spastic paraplegia in which bilateral sympathetic ramisection was performed, 13 patients suffered from chronic constipation and 11 were relieved. In a number of these a dilated colon was found at operation." Relief from chronic constipation following lumbar sympathetic ganglionectomy, in certain cases, was also reported by Adson and Brown. This operation not only divides the preganglionic fibers to the second lumbar and lower sympathetic ganglia, but also the postganglionic fibers emanating from the second, third, and fourth lumbar ganglia. Since the function of the sympathetic innervation of the large intestine above the rectum is essentially inhibitory, bilateral lumbar sympathetic ganglionectomy deprives the major portion of the large bowel of its inhibitory nerves. The pelvi-rectal (O'Beirne's) sphincter and the internal sphincter ani receive both tonic and motor impulses through the sympathetic nerves. Consequently, their relaxation is facilitated by section of the lumbar sympathetic rami.

In view of the anatomical and physiological relationships of the sympathetic innervation of the large intestine and the observed effects of lumbar sympathectomy on the tonus and motility of the large bowel, we should expect that lumbar sympathectomy would exert a beneficial effect in cases of congenital megalocolon (Hirschsprung's disease). According to the theory advanced by Hurst (1919), this disease has its underlying cause in an achalasia of the pelvi-rectal sphincter or the internal sphincter ani. This theory assumes that the peristaltic waves passing down the descending colon, which should evacuate the bowel, stop at one or the other of these sphincters by reason of its inability to relax, resulting in hypertrophy and dilatation. Fraser (1926) also regarded failure of one or the other of these sphincters to relax as a primary condition of congenital megalocolon, and advanced the opinion that this failure is due to a delay in the acquisition of the power or inhibition.

Wade and Royle (1927) reported the case of a boy, aged ten years, with congenital megalocolon, on whom Wade performed a specially designed lumbar sympathetic ramisection on the left side. In order to avoid extirpation of the lumbar ganglia and section of the peripheral rami, he cut only the white ramus joining the first lumbar ganglion and the medial rami arising from the first, second, third, and fourth lumbar ganglia, and divided the sympathetic trunk below the fourth lumbar segment.

Evacuation of the bowel could be obtained only by means of aperients or enemas in this patient before operation, and the abdomen was constantly distended. One week after operation, the abdomen was still slightly distended and aperients had to be administered in order to secure evacuation of the bowel, but in progressively diminishing doses. Three weeks after operation, the abdomen was no longer distended and evacuation of the bowel was obtained without the aid of aperients or enemas. Four months after operation the abdomen was flat and regular daily bowel movements were obtained without aid. The general condition of the patient had also improved greatly. Five months after operation, when the case was reported, daily bowel movements were still being obtained without aid and the patient's general health was good. Roentgen-ray examination also showed diminished distention of the descending and pelvic colon. The ascending and transverse portions of the colon were still larger than normal, but were assuming normal form.

Wade later reported 4 additional cases of megalocolon in which he performed similar operations. The results obtained in 2 of these cases were as satisfactory as those obtained in the case reported by Wade and Royle. The results obtained in the other 2 cases were unsatisfactory. In commenting on the latter cases, Wade stated that they were difficult cases to treat and that there was uncertainty regarding the completeness of the operation.

Judd and Adson (1928) recently reported 2 cases of congenital megalocolon in which Adson performed lumbar ganglionectomy and ramisection. In the first patient, a child (boy) nearly two years of age, the second, third, and fourth lumbar ganglia with the intervening portions of the sympathetic trunk were removed on the left side only. In the second patient, a boy, aged six years, the second, third, and fourth lumbar ganglia with the intervening portions of the sympathetic trunk were removed bilaterally. The results were entirely satisfactory in both cases.

The value of sympathectomy in the treatment of congenital megalocolon cannot be judged on the basis of the early results observed in the limited number of cases reported. The results obtained in these cases are significant, however, and the application

of sympathectomy in the treatment of this disease is fraught with far-reaching possibilities.

Sympathectomy in the Treatment of Hyperhidrosis.—Cessation of perspiration in the cutaneous area supplied from the sympathetic ganglia or through the communicating rami in question is a constant, result of sympathetic ganglionectomy or ramisection. For example following extirpation of the lumbar sympathetic ganglia or section of the corresponding communicating rami, the skin of the legs and feet remains dry. Likewise, extirpation of the superior cervical sympathetic ganglion results in cessation of perspiration on the same side of the head and face. These results show clearly that the sweat glands are supplied by secretory fibers of sympathetic origin and suggest the rationality of sympathectomy in the treatment of hyperhidrosis.

Obviously, surgical intervention in the treatment of hyperhidrosis should be considered only in extreme cases. Such a case was recently reported by Braeucker (1928). The patient, a young woman, was rendered unfit for the ordinary occupations of life and suffered general weakness by reason of excessive sweating of the hands and feet. Following section of the communicating rami of the eighth cervical and first thoracic nerves on the left side, the skin of the left arm and hand remained free from perspiration. The same result was obtained later in both legs and feet by section of the communicating rami of the fourth and fifth lumbar and first and second sacral nerves on both sides. Excessive sweating of the right hand still continued, but the general condition of the patient was improved.

Sympathectomy in the Treatment of Visceral Pain.—Sympathectomy has during recent years been employed in a limited number of cases for the relief of pain of visceral origin. Bittmann (1926) reported 9 gynecological cases in which he decorticated the abdominal aorta for a stretch of 8 to 12 cm., including 4 cm. of the common iliac arteries, for the relief of pain in the lumbar region, with complete success in every case. This result apparently confirmed his assumption that the pains were due to visceral neuroses. His operative procedure was based on the assumption that interruption of the aortic plexus, supplemented by removal of the inferior mesenteric ganglia, would block the efferent impulses and thus prevent the pain reflex. Pieri (1928) reported 34 cases in which he carried out sympathetic ramisection for the relief of visceral pain arising in various internal organs, viz.: stomach, intestine, pancreas, biliary tract, kidney, testis, bladder, adnexa, and uterus, with a high percentage of success. He regards sympathetic ganglionectomy as unnecessarily drastic for the purpose of relieving visceral pain and, therefore, recommends section of the communicating rami through which the viscus in question is supplied. In many instances,

unilateral ramisection is sufficient. For example, pain of gastric origin is usually relieved by intervention on the right side only. Barden and Leuret (1928) also reported a case of severe gastric crises which was completely relieved by section of the communicating rami of the ninth, tenth, and eleventh thoracic nerves. Barnard and Theodoresco (1928) reported section of the pelvic sympathetic nerves in 8 cases of advanced pelvic carcinoma, with complete relief from pain in some cases and partial relief in others.

Obviously, sympathetic ramisection for the relief of visceral pain should be considered only in extreme cases, *e. g.*, the gastric crises of tabes, particularly when they are characterized by colicky pains, renal neuralgia of the clinical type which presupposes the absence of anatomical changes, and certain severe pelvic neuralgias. According to Barnard and Theodoresco, the principal indications for section of the pelvic sympathetic nerves are pelvic pains which cannot be explained on the basis of gross pathological lesions, and the pain of advanced pelvic carcinoma. The relief of visceral pain following sympathetic ramisection, in such cases, probably is due mainly to interruption of afferent conduction pathways. The interruption of efferent fibers probably is a factor in some cases by reason of consequent vasomotor changes. Nevertheless, the operation cannot be regarded as a curative, but only as a palliative measure.

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CHAPTER XVI.

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